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# AVD

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# Annals of Vascular Diseases

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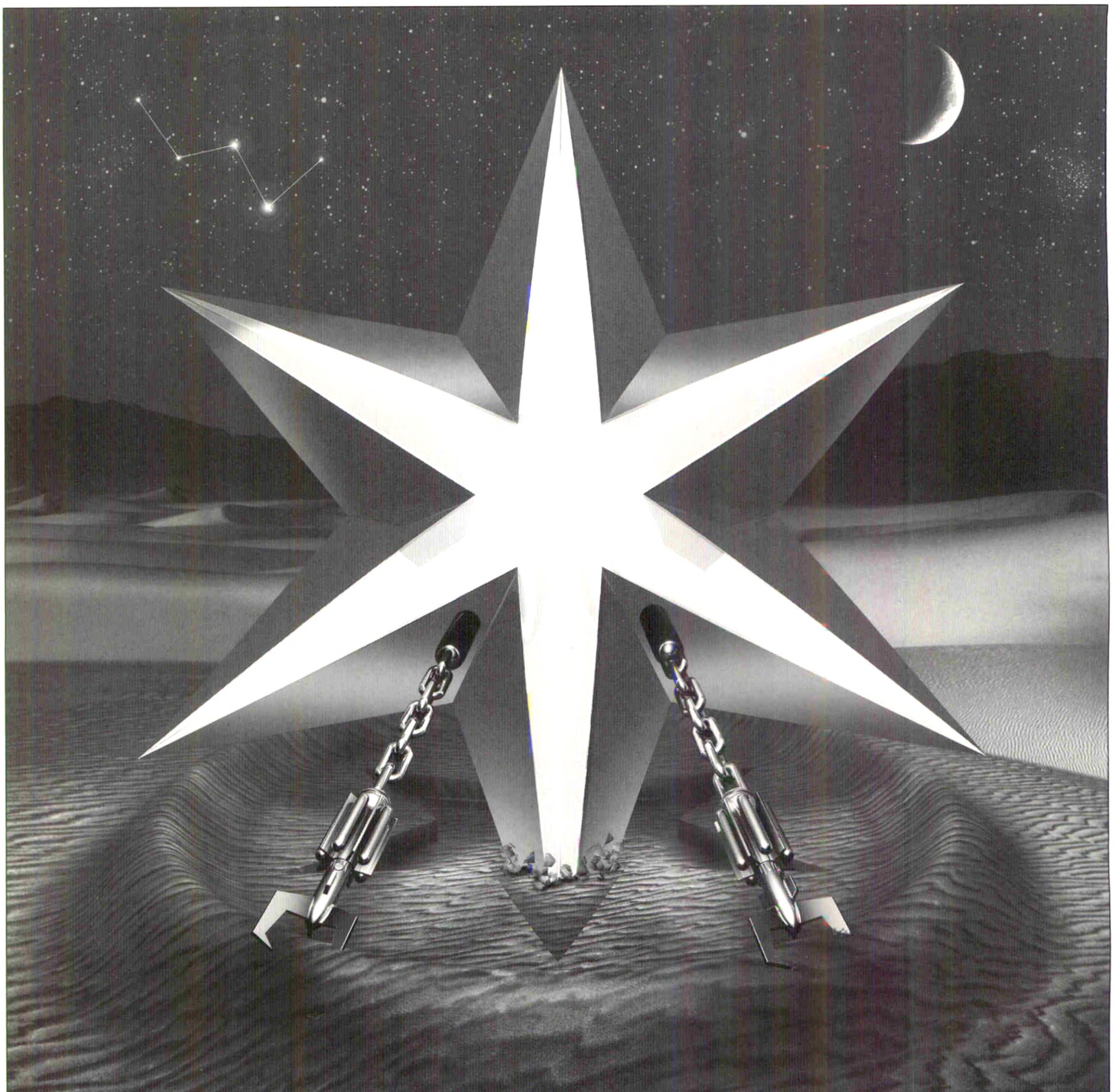

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*Asian Society for Vascular Surgery*
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# AVD
# Annals of Vascular Diseases

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*Asian Venous Forum*

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The Annals of Vascular Diseases is an emerging journal launched from Japan in 2007.
The Journal publishes peer-reviewed original articles, editorials, reviews, case reports and others in vascular research, vascular medicine, surgery, and the allied fields. Several journals dedicated to the vascular field exist in Asia including Japan. The **Japanese College of Angiology**, the **Japanese Society for Vascular Surgery** and the **Japanese Society of Phlebology**, therefore, collaborated to sponsor this new journal to jump-start the development and maturity of this growing field. Since October 2008 and June 2010, AVD has been the Official Journal of **Asian Society for Vascular Surgery** and **Asian Venous Forum** as well respectively.
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**Obituary**

# In Memory of Dr. Nobuyuki Nakajima

Dr. Nakajima passed away at the age of 76 from pancreatic cancer on October 20, 2011. He underwent surgery for obstructive jaundice that developed in the summer of 2010, and, although having returned to his clinical practice in April 2011, finally lost his battle after being treated for more than 1 year. During his lifetime, he made great efforts to publish and promote this high-quality English journal mainly focusing on vascular diseases for the first time in Asia as the first chief editor.

Being a graduate of Chiba University in 1961, he was trained in the First Department of Surgery at Chiba University Hospital, and, from 1969, he worked at the State University of New York as a resident and Wyckoff Heights Medical Center as a chief resident. After returning to Japan, he was appointed as the chief doctor in 1978 and director in 1985 of the Department of Cardiovascular Surgery at the National Cerebral and Cardiovascular Center. From 1991, he worked as a professor of the First Department of Surgery at Chiba University. He was also the chairman of the Japanese Society for Vascular Surgery for 6 years from 1999, and promoted the partnership with the European Society for Vascular Surgery and Society for Vascular Surgery of the United States, while contributing to the foundation of the World Federation of Vascular Societies as the representative of Japan and Asia. At the same time, he was a leading vascular surgeon dealing with all vascular diseases from thoracic aortic aneurysms to Buerger disease, and was involved in a broad area of research, while supervising operations in Asian countries, such as China and South Korea, to improve the level of vascular surgical practice in Asia; his contribution to the promotion of vascular surgery in Asia was considerable and great enough to create an impression that "the 21st century is the era of Asia". His devotion to Asia was based on his deep knowledge of Western countries, and, undoubtedly, he was a Japanese with a very strong love for Asia. I promise to make every effort for the further development of the Asian Society for Vascular Surgery, while heartily praying for the repose of his soul.

Hiroshi Shigematsu
President of the 13th Annual Meeting of the Asian Society for Vascular Surgery
Director of the Japanese Society for Vascular Surgery
Director of the Japanese College of Angiology

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**Original Article**

# Abdominal Aortic Disease Caused by Penetrating Atherosclerotic Ulcers

Masataka Sato, MD,[1] Akito Imai, MD,[2] Hiroaki Sakamoto, MD,[1] Akinobu Sasaki, MD,[2]
Yasunori Watanabe, MD,[1] and Tomoaki Jikuya, MD[2]

***Objective:*** **Penetrating atherosclerotic ulcer (PAU) of the aorta is defined as an atherosclerotic lesion with ulceration of the aortic intima and media and rupture of the internal elastic lamina. PAU induced aortic dissection, aortic rupture, and secular aortic aneurysm and typically occurs in elderly hypertensive patients with severe atherosclerosis. Although it has been reported that atherosclerosis similarly occurs in the abdominal aorta, its natural history and treatment are still unclear. This study investigated the clinical features, natural history, and treatment of PAU of the abdominal aorta.**

***Method:*** **Between April 2006 and March 2009, 4 diagnoses of PAU in the abdominal aorta were made by computed tomography (CT) and magnetic resonance imaging (MRI). These 4 cases were analyzed along with 61 previously reported cases from the literature with diagnoses of PAU in the abdominal aorta, aortic rupture, and isolated abdominal aortic dissection over the past 15 years, giving a total of 65 cases.**

***Results:*** **The patients were men with an average age of 63.5 years. All 4 had hypertension, and 2 had concomitant coronary artery disease. Two patients were asymptomatic, and the other 2 were symptomatic and transmural rupture had occurred. All diagnoses were made by CT and MRI. All 4 patients underwent open surgery with a knitted Dacron graft, with no postoperative deaths. In the literature, 53% of cases were symptomatic, including pain (40%, n = 26), shock (4.6%, n = 3), and lower limb embolism (9.2%, n = 6). The remaining 40% of cases were asymptomatic (n = 26). Six patients were treated medically, while 58 patients underwent surgery, with 2 postoperative deaths.**

***Conclusion:*** **We suggest that surgical treatment (open surgery or endovascular stent grafting) should be performed to prevent an aortic catastrophe such as intramural hematoma, dissection, or rupture. (English translation of Jpn J Vasc Surg 2010; 19: 723-730.)**

***Keywords:*** penetrating atherosclerotic ulcer, saccular aortic aneurysm, isolated aortic dissection, aortic rupture

## INTRODUCTION

Penetrating atherosclerotic ulcer (PAU) is defined as an atherosclerotic lesion, with ulceration of the aortic intima and media, that penetrates the internal elastic lamina,(1) and first reported by Shennan in 1934. PAU frequently affects elderly people with marked atherosclerosis and frequently develops in the chest, particularly in the descending aorta. However, it has been reported that a similar pathological condition also occurs in the abdominal aorta, inducing isolated aortic dissection, saccular aortic aneurysms, and aortic rupture.

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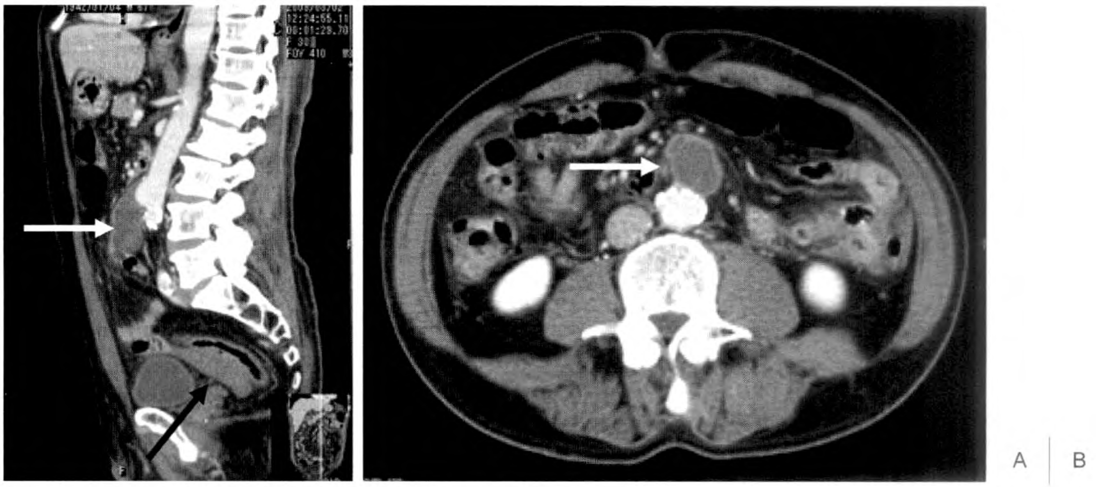

**Fig. 1** **A, B:** An abdominal computed tomography scan demonstrated a saccular aneurysm of the infrarenal abdominal aorta (white arrow) and intraperitoneal fluid collection (arrow).

## SUBJECTS AND METHODS

Between April 2006 and March 2009, we treated 76 patients with abdominal aortic aneurysm in 2 institutions, and the cause of the aneurysms was considered to be PAU in 4 patients (5.3%). Patients with infectious disease, Marfan syndrome, or a history of trauma were excluded. In the 4 patients and 61 previously reported patients with PAU/rupture/isolated dissection of the abdominal aorta in the literature (total, 65 patients), the clinical characteristics, natural history of PAU, and treatment methods were evaluated.

## RESULTS

The mean age of the 4 patients was 63.5 years. Hypertension and hyperlipidemia were observed in all and 3 patients, respectively, and had been treated with oral drugs in all patients. None of the patients had peripheral vascular disease or carotid artery lesion. One patient had a history of emergency operation for impending rupture of a thoracic aortic aneurysm.

Two patients were asymptomatic. Abdominal pain and low back pain were observed in 1 patient each. Since the patient with abdominal pain showed the acute progression of anemia and CT findings of intra-abdominal hemorrhage, strongly suggesting aortic rupture, emergency operation was performed.

The preoperative definite diagnosis was made based on CT findings in 3 patients and MRI findings in 1. In the patient diagnosed using MRI, CT was avoided due to moderate renal dysfunction and a history of suspected contrast agent allergy. In the patient with intra-abdominal bleeding (Patient 1), there was a saccular aneurysm with a thrombotic cavity that anteriorly protruded from the abdominal aorta at the level of the third lumbar vertebra but no findings suggesting bleeding in the retroperitoneal space around the aorta (**Fig. 1**). In Patient 2, a saccular aneurysm protruding to the lumbar vertebral body was observed, and its cavity was almost thrombosed (**Fig. 2**).

All patients underwent replacement with a knitted Dacron graft. No stent graft was used in any patient. Vascular reconstruction was performed using a straight graft in 3 patients and a bifurcated graft in 1, but reconstruction of the renal artery or IMA was not performed in any patient. During the operation, aortic or aneurysmal rupture was observed in 2 patients. There was no hematoma in the retroperitoneal space in the 2 patients with rupture; direct bleeding into the intra-abdominal cavity was observed in 1 patient, and penetration into the lumbar vertebral body, in the other.

Mycotic aneurysm was denied in all patients by pre- and intraoperative examinations. Pathological examination revealed marked atherosclerotic changes such as atheroma formation and cholesterin crystal deposition in the aortic intima, almost complete rupture of the intima and media, and replacement of all layers by fibrous tissue in Patients 1 and 3 (**Fig. 3**). In Patient 2, histopathological evaluation was inadequate because of the absence of the aneurysmal wall, but it revealed hyaline thickening of the intima of the aortic wall, marked atheromatous changes, and calcification, indicating severe atherosclerotic changes.

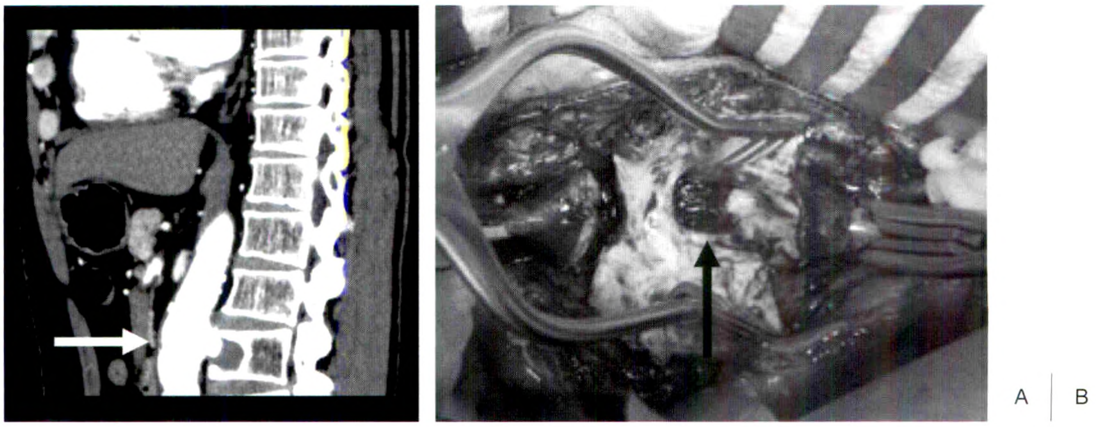

**Fig. 2** **A**: Computed tomography (CT) of the abdominal aorta demonstrated a saccular abdominal aortic aneurysm that penetrated to the lumbar vertebra (white arrow).
**B**: Focal perforation of the intima and thrombus in the saccular aneurysm (arrow).

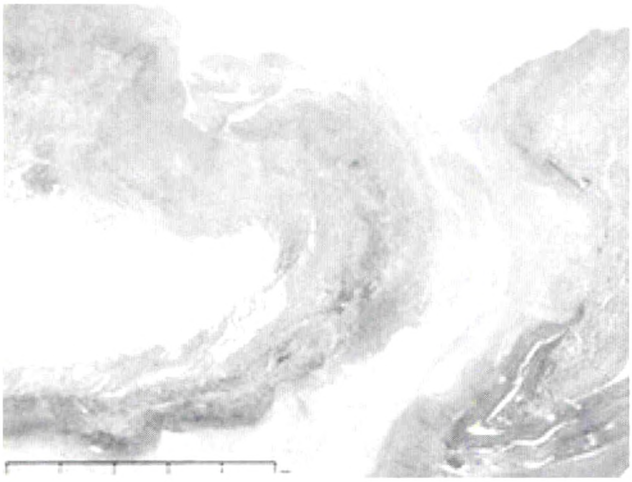

**Fig. 3** Photomicrogram of the aneurysm wall (case 1) with Elastica van Gieson stain demonstrated that the intima and the medial elastic fiber were interrupted at the margin of the aneurysm.

In Patient 4, histopathological examination was not performed. No perioperative complications developed. All patients showed a favorable postoperative course and were discharged. To the present, 6–15 months after the operation, none of the patients has had any notable problems.

The clinical characteristics of our 4 patients are shown in **Table 1.**

Our patients and the 61 previously reported patients with PAU / aortic rupture / isolated dissection of the abdominal aorta during the previous 15 year period in the literature (total, 65 patients) were evaluated. There have been many reports of isolated abdominal aortic dissection, but acute, iatrogenic, or traumatic cases were excluded since this was a study on PAU. Hypertension was observed as a complication in 60% of the patients, and coronary artery disease and peripheral vascular disease in 23% each. Symptoms were present in 53% of the patients, and abdominal pain, low lumbar pain, and shock due to aneurysmal rupture or impending rupture were frequently observed. There was also lower limb embolism with PAU as its source in 9.2% (n = 6). 40% (n = 26) of the patients were asymptomatic. The diagnosis was made using CT in many patients (88%, n = 57), but angiography and MRI were also useful for diagnosis. Concerning treatment methods, the course was observed with drug administration in 7 patients, of whom 1 died during the course observation. The other 58 patients (89%) were actively treated by open surgery (46%, n = 30) or stent grafting (43%, n = 28). Two patients died during the perioperative period. One of them was in shock before the operation, and developed intestinal necrosis after the operation and died of sepsis. The other developed aortic-duodenal fistulation, underwent surgery twice, transiently improved, but subsequently developed pneumonia, and died of sepsis 4 months after the initial operation.

Characteristics of 65 patients are shown in **Table 2.**[2–25)]

## Discussion

In 1986, Stanson et al. defined PAU as "an atherosclerotic lesion with ulceration in the vascular wall that penetrates the internal elastic lamina and media."[1)] Classically, PAU was considered to frequently occur in the descending aorta in elderly people with marked

**Table 1 Clinical characteristics of the four patients in this study**

| Patient | Sex, age | Presenting symptoms | Associated vascular disease | Associated aneurysm | Diagnosis | Treatment | Outcome (mo) |
|---|---|---|---|---|---|---|---|
| 1 | M, 67 | abdominal pain<br>anemia | - | - | CT | straight graft | alive (6) |
| 2 | M, 61 | none | CAD | thoracic aorta | CT | straight graft | alive (15) |
| 3 | M, 61 | none | CAD | - | MRI | bifurcated graft | alive (15) |
| 4 | M, 67 | lumbar pain | - | - | CT | straight graft | alive (15) |

CAD: coronary artery disease

atherosclerosis. However, atherosclerotic changes also frequently develop in the abdominal aorta as well as the thoracic descending aorta, and abdominal aortic diseases due to PAU have also been reported.[1–27] The progression of PAU induces saccular aneurysms, aortic dissection, or aortic rupture. In particular, in the abdominal aorta, aneurysm formation is considered to occur more readily than dissection.[2,10] Differentiation among these complications, as well as PAU, is often difficult, and there is a mixture of various pathological conditions. Batt et al. and Tsuji et al. stated that an ulcerative lesion not extending beyond the aortic wall on angiograms or CT images should be added to the definition of PAU.[2,16] Therefore, saccular aneurysm, aortic rupture, and isolated abdominal aortic dissection are complications due to the progression of PAU. Isolated dissection was observed in 1 of our 4 patients and a saccular aneurysm in 3 patients, of whom 2 developed aortic rupture. In a strict sense, these conditions are complications of PAU. In this study, 30% had PAU without complications while 70% showed complications such as a saccular aneurysm, IMH, aortic rupture, or aortic dissection.

For the diagnosis of PAU, ulcer visualization using angiography was conventionally considered being useful. Stanson et al. performed angiography of the thoracic aorta in 684 patients, and observed PAU in 2.3%.[1] However, since evaluation is performed in only one direction, and evaluation of the aortic wall is impossible with angiography, lesions might be overlooked. At present, CT allows the rapid and straightforward evaluation of the aortic cavity and wall and diagnosis based on medial deviation of intimal calcification and the presence of an intramural hematoma lateral to the calcification. In this study, the lesion was diagnosed using CT in many patients (89%). PAU is a pathological condition in the presence of systemic atherosclerosis as a predisposing factor, and therefore, can be multiple. Tsuji et al. described the necessity of complete evaluation of the aorta once PAU was detected.[16] Multi-detector CT, recently developed, may be particularly useful for diagnosis because extensive, detailed information on the aorta can be straightforwardly obtained. In addition, MRI has been reported to be helpful in diagnosis because the signal intensity of the aortic wall increases in the presence of PAU on both T1- and T2-weighted images.[16,19]

The natural history of PAU is still unclear, and opinions are also divided concerning the timing of treatment. Emergency operation is naturally necessary in patients showing persistent abdominal symptoms, a rapid increase in PAU, or unstable hemodynamics. However, some studies have shown a favorable prognosis of PAU that is frequently observed in elderly people even without active treatment. As shown by the pathological tissue of our patients, the intima and media of the aortic wall had been almost ruptured in saccular aneurysms due to PAU, increasing the risk of bleeding compared with common fusiform aneurysms. Goldstein et al. reported a case of PAU that ruptured 1 month after diagnosis.[4] Quint et al. followed up 38 patients with PAU (56 sites) using CT, and reported the progression of PAU and development of complications in 1/3 of the patients, suggesting difficulty in predicting the course of PAU based on CT findings.[12] Concerning saccular aneurysms, Vorp et al. reported the importance of the shape and symmetry, in addition to size, to evaluate the risk of rupture and stress on the arterial wall.[28] Hollier et al. recommend surgery for asymmetrical saccular aneurysms due to the risk of rupture irrespective of their size.[29]

In 2 of our patients, aortic rupture occurred, and aortic or aneurysmal rupture was observed in 23% (n =15) of all patients including those in the literature evaluated in this study. Therefore, we consider that treatment should be initiated as early as possible in relatively young active patients. As another cautionary item, in Patient 1, since preoperative CT revealed no hematoma around the saccular aneurysm or abdominal aorta and the presence

**Table 2** Characteristics of 65 PAUs of the abdominal aorta, aortic rupture, and isolated abdominal aortic dissection (review of the literature and this study)

| Author (year) | N (65) | Age, sex | Comorbid condition | | | Sign at presentation | | | | Diagnosis | | | Treatment | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | HT | CAD | PVD | Pain | Shock | Embolism | None | CT | Angio | MR | | |
| Origuchi (1996) | 4 | 59, 3M1F | 1 | - | - | 4 | - | - | - | 4 | - | 1 | 4 OS | 3 alive, 1 death |
| Goldstein (1997) | 1 | 67, M | 1 | 1 | - | 1 | - | - | - | 1 | - | - | OS | alive |
| Does (1997) | 2 | 63, 1M1F | - | 1 | - | 2 | 1 | - | - | - | 1 | - | 2 OS | 1 alive, 1 death |
| Raymond (1997) | 1 | 74, M | - | - | - | 1 | - | - | - | 1 | - | - | OS | alive |
| Moriyama (1998) | 1 | 74, M | 1 | - | - | - | - | - | 1 | 1 | 1 | - | OS | alive |
| Ferko (1998) | 2 | 60, 2M | 1 | - | - | - | - | - | 2 | 2 | 2 | - | 2 SG | 2 alive |
| Taylor (1999) | 2 | NA | NA | NA | NA | - | - | - | 2 | 2 | - | - | 2 OS | 2 alive |
| Ruckert (1999) | 1 | 52, M | - | - | - | - | - | - | 1 | 1 | 1 | - | OS | alive |
| Eggebrecht (2001) | 1 | 70, M | 1 | - | - | - | - | - | 1 | 1 | 1 | - | SG | alive |
| Quint (2001) | 6 | NA | NA | NA | NA | NA | NA | NA | NA | 6 | - | - | 6 Med | 5 alive, 1 death |
| Toda (2001) | 2 | 70, M | 2 | - | - | 2 | - | - | - | 2 | 2 | - | 2 OS | 2 alive |
| Geza (2002) | 1 | 55, M | 1 | - | - | - | - | - | 1 | 1 | - | - | OS | alive |
| Farber (2002) | 1 | 57, M | 1 | - | 1 | - | - | - | 1 | 1 | - | - | Med | alive |
| Tsuji (2003) | 4 | 78, 4M | 4 | 2 | - | 3 | - | - | 1 | 2 | - | 2 | 4 SG | 4 alive |
| Vasquez (2003) | 1 | 81, M | 1 | - | - | 1 | - | - | - | 1 | - | - | SG | alive |
| Ventura (2003) | 1 | 68, F | 1 | - | - | 1 | - | - | - | 1 | - | - | OS | alive |
| Minor (2003) | 2 | 55, 2M | 2 | 1 | 1 | 1 | - | - | 1 | 2 | 1 | 1 | 2 OS | 2 alive |
| Flores (2004) | 2 | 66, 1M1F | 2 | 1 | - | 1 | - | - | 1 | 3 | - | - | 2 OS | 2 alive |
| Batt (2005) | 8 | 70, 7M1F | 4 | 3 | 6 | 4 | 1 | 1 | 2 | 4 | 4 | - | 5 OS, 3 SG | 8 alive |
| Borioni (2005) | 2 | 76, 2M | 2 | - | - | - | - | 2 | - | 2 | - | - | 2 SG | 2 alive |
| Caronno (2006) | 1 | 81, M | 1 | - | - | - | - | - | 1 | 1 | - | - | SG | alive |
| Thalheimer (2007) | 1 | 57, M | 1 | 1 | 1 | 1 | - | - | - | 1 | - | - | SG | alive |
| Piffaretti (2007) | 13 | 73, 12M1F | 13 | 2 | 6 | 2 | 1 | 3 | 8 | 13 | - | - | 13 SG | 12 alive, 1 death |
| Tsuji (2007) | 1 | 69, M | 1 | 1 | - | - | - | - | 1 | 1 | 1 | - | OS | alive |
| Present study | 4 | 64, 4M | 4 | 2 | - | 2 | - | - | 2 | 3 | - | 1 | 4 OS | 4 alive |
| Total | 65 | | 45 | 15 | 15 | 26 | 3 | 6 | 26 | 57 | 14 | 5 | 30 OS, 28 SG, 7 Med | |

HT: hypertension; CAD: coronary artery disease; PVD: peripheral vascular disease; OS: open surgery; SG: stent graft; Med: medical treatment; NA: not available of only ascites in the abdominal cavity, the diagnosis of aneurysmal rupture was difficult. In this patient, mass bleeding could be avoided due to intra-aneurysmal hematoma. However, the possibility that saccular aneurysms penetrate directly into the abdominal cavity, not bleeding into the retroperitoneal cavity, depending on the aneurysmal extension direction should be taken into consideration.

Isolated abdominal dissection is rarely observed compared with aneurysms, accounting for 0.4%–2% of all aortic dissections.14,21,22) This tendency is due to a decrease in elastin in the aortic wall from the chest to the abdomen.20) However, in the abdominal aorta unlike the thoracic aorta, changes in the media such as cystic medial necrosis rarely occur, and the presence of PAU may be closely associated with the development of abdominal aortic dissection. The onset of this dissection is often acute with symptoms such as abdominal and low back pain, but some cases are asymptomatic and incidentally detected. In some cases, there is no pain associated with dissection itself, and the dissection is manifested by branch ischemia due to the false lumen.22) Invasive treatment such as surgery and stent grafting are indicated in acute or symptomatic cases, but course observation including periodical evaluation using imaging techniques is recommended for asymptomatic or chronic cases.14) In our patient with isolated dissection, the course was observed, but surgery was selected due to its rapid increase after 1 year. However, there are no clear indications for surgery when isolated dissection leads to aneurysm formation, the risk of rupture is high compared with true aneurysms.10,14,22) Therefore, irrespective of the size, carefully observation is necessary.

As another complication, thrombosis in the ulcer, causing thromboembolism in the peripheral artery, has also been reported. In this study, lower limb arterial thrombosis with PAU as the thrombosis source was observed in 9.2% (n = 6). When there is no cardiogenic thrombosis source, the necessity of suspecting the presence of PAU as a cause of embolism has also been suggested.2,30)

Concerning treatment methods, anatomical vascular reconstruction using vascular grafts, are generally performed. In recent years, stent grafts have been introduced, and treatment experiences with them for PAU and saccular aneurysms have been reported. Since the lesions of PAU, saccular aneurysms, or isolated abdominal dissection are localized, an adequate landing zone can be obtained. Therefore, compared with fusiform aneurysms, the risks of migration and endoleak as complications specific to stent grafting decrease.2,8,11,16,17,21,24) In the future, stent grafting as well as surgery will be a treatment choice based on the patient's general condition and preoperative activity.

## CONCLUSIONS

We reported 4 patients with abdominal aortic disease caused by PAU, along with a review of the literature.

PAU was conventionally considered to frequently develop in the thoracic aorta, but it may be a severe lesion that can similarly occur in the abdominal aorta and cause aortic dissection, saccular aneurysm, or aortic rupture. Patients with symptoms such as chest/abdominal pain or low back pain and those showing a rapid increase in PAU should be treated as soon as possible if they can tolerate surgery. Surgery should be recommended to patients with saccular aneurysms, and strict course observation is necessary in those with isolated dissection.

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**Original Article**

# Surgical Treatment for Thoracic Aneurysms: Comparison of Stent Grafting and Open Surgery

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***Objectives:*** **Early and mid-term results of stent graft (SG) treatment for thoracic aortic aneurysms (thoracic endovascular aneurysm repair: TEVAR) were retrospectively compared with open surgical treatment.**
***Methods:*** **The records of 213 patients in whom single thoracic aortic aneurysm repairs had been performed in our department from January 2006 through August 31, 2009 were reviewed. Acute aortic dissection was excluded. Each case was reviewed for indications for TEVAR from an anatomical standpoint. Among 62 cases in which TEVAR was indicated, 30 (SG group) were treated by TEVAR and 32, by open surgery (OP group). Early and mid-term results were analyzed retrospectively in both groups.**
***Results:*** **There were no operative deaths in either group. The SG group demonstrated significantly less operative bleeding, a shorter operative time, and shorter postoperative hospital stay compared with the OP group. There were 3 deaths in the SG group and 4 in the OP group, which occurred within an average of 656.4 days during the follow up period. The 3 year actuarial survival rate was 88.7% in the SG group and 87.1% in the OP group, and there were no significant differences between the groups.**
***Conclusion:*** **Although early and mid-term results of TEVAR and open surgery were similar, TEVAR is generally less invasive and may be preferable for high-risk patients, compared with open surgical repair. (English Translation of Jpn J Vasc Surg 2010; 19: 51-56.)**

***Keywords:*** thoracic aortic aneurysm, vascular surgery, endovascular surgery

## INTRODUCTION

With advances in medical techniques in recent years, surgical treatment for thoracic aneurysms has markedly improved. The indications for surgery have expanded to patients with complications and elderly patients, and surgery has been actively performed. In 2008, commercially available SG devices for thoracic aneurysms began to be covered by insurance in Japan, and treatment choices have increased. Therefore, the indications for stent grafting (SG) for thoracic aneurysms are expected to expand further.

Open surgery for thoracic aneurysms is an almost established method. However, in many cases, its invasiveness requiring thoracotomy and extracorporeal circulation is a problem. On the other hand, since SG (thoracic endovascular aneurysm repair: TEVAR) is a new treatment method, its long-term results are still unclear. At present when there are many treatment choices, the indications for both should be adequately considered, and the most appropriate treatment strategy for each patient should be selected. Although some studies have shown the superiority of TEVAR, it is unclear whether open surgery was selected for lesions strictly indicated for TEVAR.[1, 2)]

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**Table 1 Reasons for stent graft choice**

| Major specific indication | Number | % |
|---|---|---|
| Patient request | 9 | 30.0 |
| Advanced age | 5 | 16.7 |
| Cardiopulmonary disorder | 4 | 13.3 |
| Advanced age • post-thoracotomy | 3 | 10.0 |
| Central nerve disorder | 3 | 10.0 |
| Post-thoracotomy | 2 | 6.7 |
| Multiple aneurysms | 2 | 6.7 |
| Dialysis | 1 | 3.3 |
| Cancer | 1 | 3.3 |

We retrospectively evaluated early and mid-term treatment results in patients in whom both TEVAR and open surgery could be anatomically selected, and compared the two surgical methods.

## SUBJECTS AND METHODS

We performed a retrospective study in 213 cases with a single thoracic aneurysm excluding acute aortic dissection, who were surgically treated in our hospital between January, 2006 and August 31, 2009. All cases were classified according to the location of the lesion, and sizing of the SG device was performed. SG was indicated in whom the landing zone could be ≥15 mm from the left common carotid artery on the proximal side and ≥15 mm from the celiac artery on the distal side, the arterial diameter at the landing zone was 20–38 mm, and excessive calcification was absent. Of the 213 patients, 62 (29.1%) had indications for SG in our center. When these patients were classified according to the actually selected treatment, 30 patients were classified as the TEVAR group (SG group) and the other 32 as the open surgery group (OP group). The both groups were retrospectively evaluated.

For TEVAR, the Tokyo Medical University (T.M.U.) type SG device (Najuta, Kawasumi Laboratories, Tokyo) was introduced in 2006, and a commercially available SG device (TAG® W.L. Gore, USA) was introduced in January 2008. Before the introduction of the commercially available SG device, open surgery was the first choice. After the introduction of the SG device, SG was recommended as the first choice to high-risk patients such as those with many comorbidities, but the surgical method was finally selected by patients and their families with adequate, informed consent. Preoperative respiratory disorders were defined as those that require take-home oxygen therapy or treatment for respiratory dysfunction on an outpatient basis. Postoperative respiratory disorders were defined as those that require controlled ventilation ≥72 hours after surgery.

All values are expressed as the mean plus standard deviation, and statistical differences were analyzed using Student's t-test and the $\chi^2$ test. The survival rate was analyzed using the Kaplan-Meier and Log-rank methods. $P < 0.05$ was regarded as significant.

## RESULTS

### 1. Patient background

The reasons for the selection of SG in the 30 cases in the SG group are shown in **Table 1**. SG was selected due to high risk in 21 cases (70%). The most frequent reason was the patients' wish, which was observed in 9 cases (30%). These results did not always reflect our selection criteria.

A T.M.U. type Najuta was used in 23 of the 30 cases and a TAG® in 7. The proximal landing was further than Zone 4 in 21 patients; the other 9 cases needed a proximal landing zone from Zone 0 to Zone 3. In the OP group, replacement of the descending aorta via left thoracotomy was performed in 25 of 32 cases, and total arch replacement using the median sternotomy, in 7. In all cases in this group, extracorporeal circulation was used. Four cases of descending aorta replacement performed at a normal temperature and the other 17 cases were performed under hypothermic circulatory arrest. In the 7 cases who underwent total arch replacement, the minimum core temperature was 25°C, and distal circulatory arrest/antegrade selective cerebral perfusion was used as the standard procedure.

As shown in **Table 2**, there were no significant differences in the mean age, male/female ratio, presence/absence of atherosclerosis risk factors, preoperative respiratory dysfunction, emergency operation, or the history of open heart surgery, between the SG and OP groups.

### 2. Early results

There were no operative deaths in either group, and all cases in both groups were discharged on foot or transferred to another hospital. Postoperative cerebral infarction was observed in 3 cases in the OP group, paresis in 2, in the SG group, and paraplegia in 1, in the OP group. However, these conditions improved after rehabilitation, and their incidence did not significantly differ between the two groups. The operation time, period (days), until the initiation of postoperative oral intake, and

**Table 2 Preoperative data**

| | SG group (n = 30) | OP group (n = 32) | *P* value |
|---|---|---|---|
| Age (y.o.) | 70.1w14.1 | 69.6w10.7 | 0.89 |
| Gender (male: female) | 25: 5 | 24: 8 | 0.41 |
| Hypertension | 12 | 15 | 0.92 |
| Diabetes | 4 | 5 | 0.72 |
| Chronic renal failure (Cr>1.5) | 3 | 2 | 0.34 |
| Chronic respiratory disorder | 6 | 3 | 0.24 |
| History of thoracotomy | 5 | 4 | 0.64 |
| Emergency | 3 | 4 | 0.60 |

SG: stent graft; OP: open surgery

**Table 3 Perioperative data and morbidity**

| | SG group (n = 30) | OP group (n = 32) | *P* value |
|---|---|---|---|
| Replacement of the arch | N/A | 7 | |
| Replacement of the descending aorta | N/A | 25 | |
| Involvement of Zone 0–3 (+) | 9 | N/A | |
| Involvement of Zone 0–3 (–) | 21 | N/A | |
| Operative time (min) | 198.3w87.9 | 413.1w121.9 | <.001 |
| Operative bleeding (ml) | 154.2w167.48 | 1002.3w895.1 | <.001 |
| Blood transfusion (%) | 3 (10.0%) | 19 (59.4%) | <.001 |
| Postoperative controlled ventilation (day) | 1.0w0.0 | 3.41w3.9 | 0.016 |
| Postoperative oral ingestion (day) | 1.1w0.4 | 6.71w11.9 | 0.013 |
| Cerebral infarction (%) | 0 (0.0%) | 3 (9.3%) | 0.051 |
| Paraplegia (%) | 2 (6.6%) | 2 (6.2%) | 0.70 |
| Postoperative hospital stay (day) | 12.4w7.1 | 30.0w26.1 | <.001 |
| Operative mortality | 0 | 0 | N/A |

SG: stent graft; OP: open surgery

the postoperative hospital stay (days) were significantly shorter in the SG group, and the bleeding volume was significantly smaller in the SG group. The percentage of blood transfusion and the incidence of postoperative respiratory dysfunction were significantly lower in the SG group. Thus, the SG group was superior to the OP group, in terms of early results (**Table 3**).

### 3. Mid-term results

During the follow-up period, for a mean of 656.4 w 547.8 days, 3 cases in the SG group and 4 in the OP group died or dropped out, but no significant differences were observed between the two groups (*P* = 0.89). The 3 year survival rate was 88.7% in the SG group and 87.1% in the OP group (**Fig. 1**). The cause of death was pneumonia/respiratory dysfunction in 2 cases, malignant tumors in 2, multi-organ failure in 2, and hematemesis, resulting in sudden death, in 1.

Events considered being associated with aneurysms were observed in 1 case in the SG group. In the above patient who died of hematemesis, even though the aneurysm at the original treatment site had decreased in size, a new aneurysm formed central to the SG area and appeared to have ruptured into the esophagus. The exact cause of death was unclear, but infection of the SG device was strongly suspected. In 2 patients in the SG group, Type II endoleak persisted from immediately after the operation, and their courses have been strictly observed on an outpatient basis despite no changes in the aneurysmal diameter. There have been no cases undergoing open surgery after TEVAR or additional TEVAR.

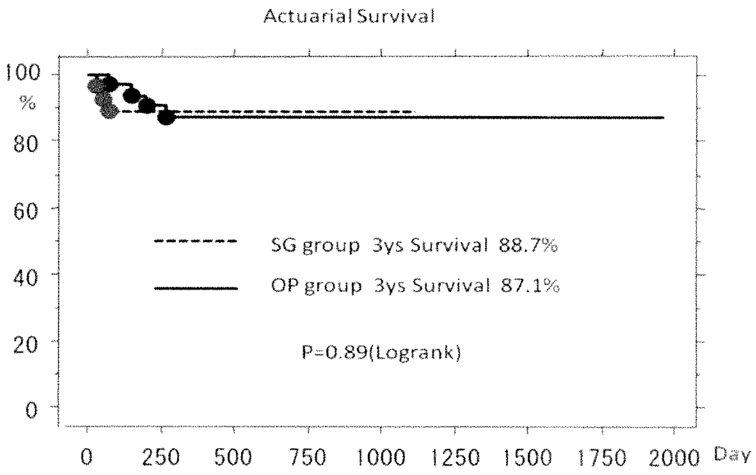

**Fig. 1** Kaplan-Meier Survival Curves for the each group.

## DISCUSSION

In Japan, as SG devices for thoracic aneurysms, TAG® (W.L. Gore, USA) and TALENT (Medtronic, USA) began to be covered by insurance in 2008 and have been used to the present. In addition, clinical trials on T.M.U. type Najuta are in progress, in 11 institutions in Japan, and this device is also expected to be covered by insurance in the future. After the introduction of these devices, treatment choices for thoracic aneurysms have increased. According to the survey of the number of surgically treated cases conducted by the Japanese Society for Vascular Surgery, surgery for aneurysms in the descending aorta was performed in 683 cases in fiscal year 2006, 922 cases in 2007, and 1214 cases in 2008, showing a marked increase. Of 1214 cases, 682 (56.2%) were treated by TEVAR. These values indicate the involvement of an increase in the number of cases treated by TEVAR, and a rise in the total number of surgically treated cases. However, the number of cases treated by TEVAR has been increasing without a general consensus regarding the relative merits between open surgery and TEVAR and criteria for the selection of treatment.

Some studies that compared the groups treated by open surgery or TEVAR in other countries have shown the superiority of TEVAR in short-mid-term results.[1–3] In Japan, a study, which compared the two methods using a home-made device for lesions located in the same area, showed good early-mid-term results after both open surgery and TEVAR, but a significantly higher mid-long-term incidence of aneurysm-related events after TEVAR.[4] In this study, in the TEVAR group, the early operative death rate was 2.5% (1 of 40 patients), but the mid-term incidence of aneurysm-associated events that occurred during 3 years was 17.9%, which was a high rate, compared with conventional open surgery. Thus, long-term follow-up is important even at present when there are commercially available devices.

Although this was a retrospective study, the open surgery and SG groups were very similar when the lesion localization and patient background were compared. No operative death was observed in either group, and early treatment results were favorable in both groups. However, postoperative cerebral infarction was observed in the open surgery group, but not in the SG group. In addition, the SG group showed a significantly smaller bleeding volume, significantly higher blood transfusion rate, and significantly shorter postoperative hospital stay. These results suggest that TEVAR is less invasive than open surgery.

In this study, in the SG group, aneurysm-associated death was observed mid-term after surgery, and Type II leak persisted after TEVAR, in 2 cases, who have been followed up to the present at the outpatient clinic, and in 9 of 30 cases, the SG device was placed proximal to Zone 3. In such cases, the proximal landing zone was often short, due to the presence of branches in the cervical area compared with TEVAR distal to Zone 4 (**Fig. 2**). Therefore, concerning the long-term results of TEVAR, aneurysm-associated events should be carefully analyzed by close follow-up.

The evaluation of 147 patients who underwent open surgery for aneurysms in the aortic arch, in our institution, between 2000 and April 2008, showed no operative

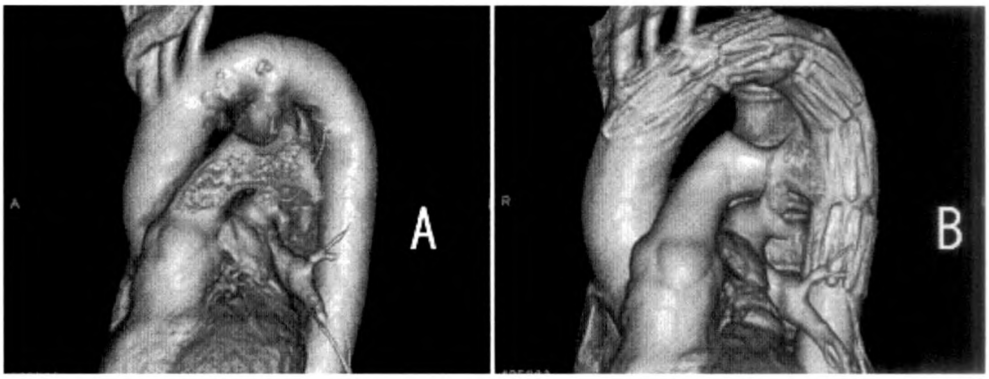

**Fig. 2** A case of TEVAR.
**A**: before deployment of SG.
**B**: after deployment of SG. The proximal landing was at Zone 1.
TEVAR: thoracic endovascular aneurysm repair; SG: stent graft

death nor postoperative cerebral infarction in 97 patients aged ≤75 years. However, in patients aged ≥75 years, the operative death rate was 10%, and the incidence of cerebral infarction was 8.3%. Based on these results, we recommend TEVAR using commercially available SG devices for high-risk patients, such as elderly patients, as the first choice and open surgery to relatively young low-risk patients, considering that the long-term results of TEVAR are still unclear. Comparison of the patients' preoperative background between the two groups in this study showed no significant difference in each item such as age. Although our policies were not always reflected, the reason for the selection of TEVAR widely varied. We recommended open surgery to 9 patients in the TEVAR group, but the patients themselves finally selected TEVAR. This suggests marked demand for minimal invasiveness at present. In addition, to reflect these results in future strategies, we intend to perform closer, long-term follow up in these patients and analyze aneurysm-associated events.

A questionnaire survey conducted in 2006 by the Japanese Association for Thoracic Surgery showed that arch replacement was performed by open surgery in 1544 (35.2%) of 4382 surgically treated patients with non-ruptured thoracic aneurysms. The number of patients who underwent this operation has been increasing. The number of patients who underwent surgery of the descending aorta was 535, also showing an annual increase. The operative death rate was 4.5% each for aneurysms in the aortic arch and those in the descending aorta, and the early results of open surgery have annually improved.5) While the surgical results have continuously improved, medical companies and workers have made great efforts to improve TEVAR devices, and their indications have gradually been expanding. To expand the indications of TEVAR to arch aneurysms, the T.M.U. type Najuta was developed in Japan, which took the lead in developing new devices, and favorable mid-long-term results have gradually been reported.6) In the future, indications for TEVAR are expected to expand further, due to an improvement in development of devices for high-risk patients in whom surgery was not conventionally indicated, and the number of surgically treated patients with thoracic aneurysms may also increase.

On the other hand, long-term results have not been adequately clarified. Makaroun et al.1) evaluated the 5 year results of TEVAR using Gore TAG and reported that the incidence of major adverse events related to open surgery was 70% immediately after surgery, 77% after 1 year, and 78.7% after 2 years, but the incidence did not increase, thereafter, until 5 years after surgery; however, that related to TEVAR using TAG was 28% immediately after the operation, 42% after 1 year, and 57.9% after 5 years, showing a slight increase. Therefore, in young patients who require long-term follow-up, the risks and benefits of TEVAR should be adequately evaluated for treatment.

## CONCLUSIONS

The early-mid-term results of both TEVAR and open surgery were favorable, but TEVAR was less invasive. While the results of open surgery have improved, devices for TEVAR have been developed. In high-risk patients, the selection of less invasive TEVAR may be appropriate. However, not all problems regarding the long-term results have been overcome. According to age and the general condition of the patient, open surgery may be the first choice. Surgical results may further improve, and indications may further expand by selecting treatment methods with consideration given to the advantages of both TEVAR and open surgery.

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**Original Article**

# Technical Challenges in Endovascular Repair of Complex Thoracic Aortic Aneurysms

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***Background:*** **Endovascular aneurysm repair has gained widespread acceptance, and there has been a significant increase in the number of aneurysms treated with stent grafts. However, the endovascular technique alone is often not appropriate for anatomically complex aneurysms involving the neck branches. We used the TAG stent for thoracic aortic aneurysms (TAA), and report our initial results.**

***Patients and Results:*** **We deployed 80 TAG stents in 65 patients electively treated with TAA between June 2006 and June 2008. Thoracic endovascular aneurysm repair (TEVAR) was performed in 45 cases of descending aortic aneurysm with no morbidity or mortality. A combination of open surgery and TEVAR was performed in 11 out of 20 cases with aneurysms of the aortic arch. The prior total arch replacement and elephant trunk procedure was performed in 3 cases with dilated ascending aorta, total debranching from ascending aorta with sternotomy in 5, and carotid-carotid artery crossover bypass in 3 cases. Meanwhile, TEVAR with coverage of the left subclavian artery was performed in the remaining 9 distal arch cases. In 3 cases with extremely short necks, a 0.018" guide wire was inserted percutaneously in a retrograde manner through the common carotid artery (CCA) into the ascending aorta to place the stent graft in close proximity to the CCA (wire protection). In 1 of these 3 cases, the TAG stent was deployed through the CCA, and the 0.018" guide wire was used to deliver a balloon-expandable stent in order to restore the patency of the CCA. In arch and distal arch aneurysm cases, perioperative mortality and the incidence of stroke were both 5.0%; dissection of the ascending aorta was seen in one case (5.0%).**

***Conclusion:*** **As treatment for descending aortic aneurysms, TEVAR can replace conventional open repair. However, TEVAR for arch aneurysms has some problems, and further improvement is necessary. (English Translation of Jpn J Vasc Surg 2010; 19: 547-555.)**

***Keywords:*** thoracic aortic aneurysm, endovascular surgery, stent graft

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## INTRODUCTION

The TAG thoracic aortic stent graft system (TAG) (W. L. Gore & Associates, Inc., Flagstaff, AZ, USA) was approved from the Ministry of Health, Labor and Welfare (MHLW) as a stent graft for thoracic aortic aneurysms (TAA) in Japan on July 2008, which may further promote the application of thoracic endovascular aneurysm repair (TEVAR). The advantages of TEVAR in this field are applicability without thoracotomy, which may be performed under local anesthesia in some cases, and a low incidence of paraplegia because aortic clamp is not necessary. However, TEVAR alone is insufficient in many cases. Herein, we report the current outcomes and problems of our TEVAR and measures taken to overcome the problems.

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**Table 1  Patients' profile**

| | | Thoracic descending aortic aneurysms | Aortic arch and distal arch aneurysms | |
|---|---|---|---|---|
| | | 45 cases | 20 cases | |
| Gender | | male 33 (73.3%), female 11 | male 16 (80%), female 4 | n.s. |
| Age | | 70.1 ± 12.2 (22–84) years | 78.6 ± 7.9 (60–94) years | $p < 0.05$ |
| Etiology | medial degeneration | 38 | 19 | |
| | dissection (ULP) | 1 | 1 | |
| | traumatic | 2 | 0 | |
| | post-CoA repair | 1 | 0 | |
| | healed mycotic | 2 | 0 | |
| | Marfan | 1 | 0 | n.s. |
| Co-morbidity | hypertension | 32 (71.1%) | 14 (70%) | n.s. |
| | cardiac diseases | 22 (48.9%) | 11 (55%) | n.s. |
| | cerebral diseases | 9 (20%) | 6 (30%) | n.s. |
| | CKD | 10 (22.2%) | 5 (25%) | n.s. |
| | COPD | 5 (11.1%) | 5 (25%) | n.s. |
| Diameter of TAA | | 60.6 ± 13.2 mm | 79.2 ± 8.3 mm | $p < 0.05$ |

ULP: ulcer-like projection; CoA: coarctation of the aorta; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; TAA: thoracic aortic aneurysm

The data are shown as the mean ± standard deviation, wherein $p < 0.05$ in Welch's t-test was considered to be significant.

## Subjects and Methods

### 1. Subjects

Seventy-three patients underwent TEVAR at our hospital during a 2-year period between June 2006 and the approval of TAG as a device for TAA. Emergency surgery for rupture was performed in 8 of them. Excluding the rupture cases, 65 cases were investigated (**Table 1**). Since the device for TAA was not approved by MHWL in Japan during this period, it was purchased by private import after approval by the Internal Review Board (IRB). For the device, TAG was used. TAA was a thoracic descending aortic aneurysm in 45 cases and arch and distal arch aneurysms in 20. There were 49 males and 16 females aged 22–94 years (mean: 71.1 ± 13.5 years). TEVAR was specified as the first choice for thoracic descending aortic aneurysms when it was anatomically applicable, and it was selected for 45 of 46 cases (97.8%). Accordingly, TEVAR was applied even for 22- and 40-year-old patients with traumatic TAA. For arch and distal arch aneurysms, open repair (aortic arch replacement) were specified as the first choice, and TEVAR was selected in 20 of 34 cases (58.8%). When the patients were divided into those with a thoracic descending aortic aneurysm and those with arch and distal arch aneurysms, the age was significantly higher, aneurysm size was greater, and more concomitant diseases were present in patients with arch and distal arch aneurysms (**Table 1**).

### 2. Surgical method

In all patients, the access route and aneurysm were evaluated by contrast CT before surgery to decide on a therapeutic indication and device size, and a treatment strategywas prepared. Basically, a treatment plan was designed to prepare an at least 20-mm-long neck on both the proximal and distal sides. Particularly, a 20-mm length of the neck on the proximal side was ensured as much as possible in arch aneurysm cases because of a disadvantage of placement in the curve region. When this was not possible, the left subclavian artery was covered to deploy a stent graft, for which communication of the bilateral vertebral arteries was confirmed by preoperative CT. When no communication was noted, bypass to the left subclavian artery was considered. When a 20-mm length of the proximal neck could not be obtained by covering the left subclavian artery, carotid-carotid artery bypass and bypass from the ascending aorta to the arch branch were considered. In surgery, one side of the common femoral artery

**Table 2 Results of TEVAR**

| | Thoracic descending aortic aneurysms | | Aortic arch and distal arch aneurysms | |
|---|---|---|---|---|
| | 45 cases | | 20 cases | |
| | TEVAR alone | 45 cases | left SCA cover | 9 cases |
| | | | partial debranching (carotid-carotid bypass) | 3 cases |
| | | | total debranching | 5 cases |
| | | | prior TAR (elephant trunk) | 3 cases |
| Mortality | 0 | | 1 (5%) | |
| Complication | 0 | | dissection of ascending aorta | 1 (5%) |
| | | | brain infarction | 1 (5%) |
| Iliac access | 3 (6.7%) | | 1 (5%) | |
| Duration of operation | 159.1 ± 78.0 min | | 292.7 ± 140.6 min | |
| Blood loss | 338.8 ± 589.3 ml | | 735.8 ± 800.0 ml | |
| Volume of contrast | 156.5 ± 66.2 ml | | 189.4 ± 88.0 ml | |
| Fluoro time | 26.3 ± 12.1 min | | 27.5 ± 10.9 min | |
| Hospital stay after TEVAR | 5.5 ± 3.7 days (1–13 median, 4.5 days) | | 15.2 ± 14.6 days (1–52 median, 9 days) | |
| Endoleak | 0 | | 2 (10%) | |

TAR: total arch replacement

was exposed, and the other side was punctured, through which a 5-F sheath was inserted. In cases with extremely tortuous and arch aneurysms, guide wire descent from the right upper limb was caught with a snare catheter inserted through the cut-down side and pulled through. A pigtail catheter was inserted through the 5-F sheath for angiography, a 20–24-F sheath was inserted through the cut-down side to deploy a stent graft, and the stent was expanded with a Tri-Lobe balloon. After confirmation byangiography, the sheath was removed and exchanged with a 9-F sheath, followed by confirmation of the absence of access route injury by angiography and intravascular ultrasonography (IVUS).

## RESULTS

### 1. Thoracic descending aortic aneurysm (Table 2)

There were 45 patients with thoracic descending aortic aneurysms. All patients were discharged without any complication. The mean operation time was about 2.5 hours, the blood loss was about 300 ml, and about 150 ml of contrast medium was used. An approach through the common iliac artery was necessary in 3 of the 45 cases (6.7%), and pull-through wire was necessary due to tortuousity in 3 (6.7%) (**Table 2**). The duration of hospital stay after treatment was about 5 days. No endoleak was noted after TEVAR in any patient.

### 2. Arch and distal arch aneurysms

Arch replacement was performed in 14 patients with arch and distal arch aneurysms because the systemic condition was favorable and indicated open repair. The remaining 20 patients were treated with TEVAR, and the left subclavian artery was covered to deploy a stent graft in 9 of the 20 cases, in which communication of the bilateral vertebral arteries was confirmed by preoperative CT, and intraoperative selective angiography was performed to confirm that the bilateral vertebral arteries were connected to the basilar arteries, respectively. Surgery was combined because of the lack of a proximal landing zone in 11 of 31 cases (**Table 2**). Carotid–carotid artery (–subclavian artery) bypass was applied in 3 (**Fig. 1**), total debranching from the ascending aorta was applied in 5 (**Figs. 2** and **3**), and 2-stage TEVAR with prior ascending arch replacement with an elephant trunk in 3 (**Fig. 4**, **Table 2**). To deploy a stent graft in the closest proximity to the left common carotid artery, the carotid artery was percutaneously punctured and 0.018" guide wire was inserted and advanced to the ascending aorta, followed by stent graft deployment (carotid puncture wire protection method) in 3 cases (**Fig. 5**). In one of these, an Express Stent (Boston Scientific) was retrogradely deployed in the left common carotid artery because this artery was covered.

Approaches through the common iliac artery and

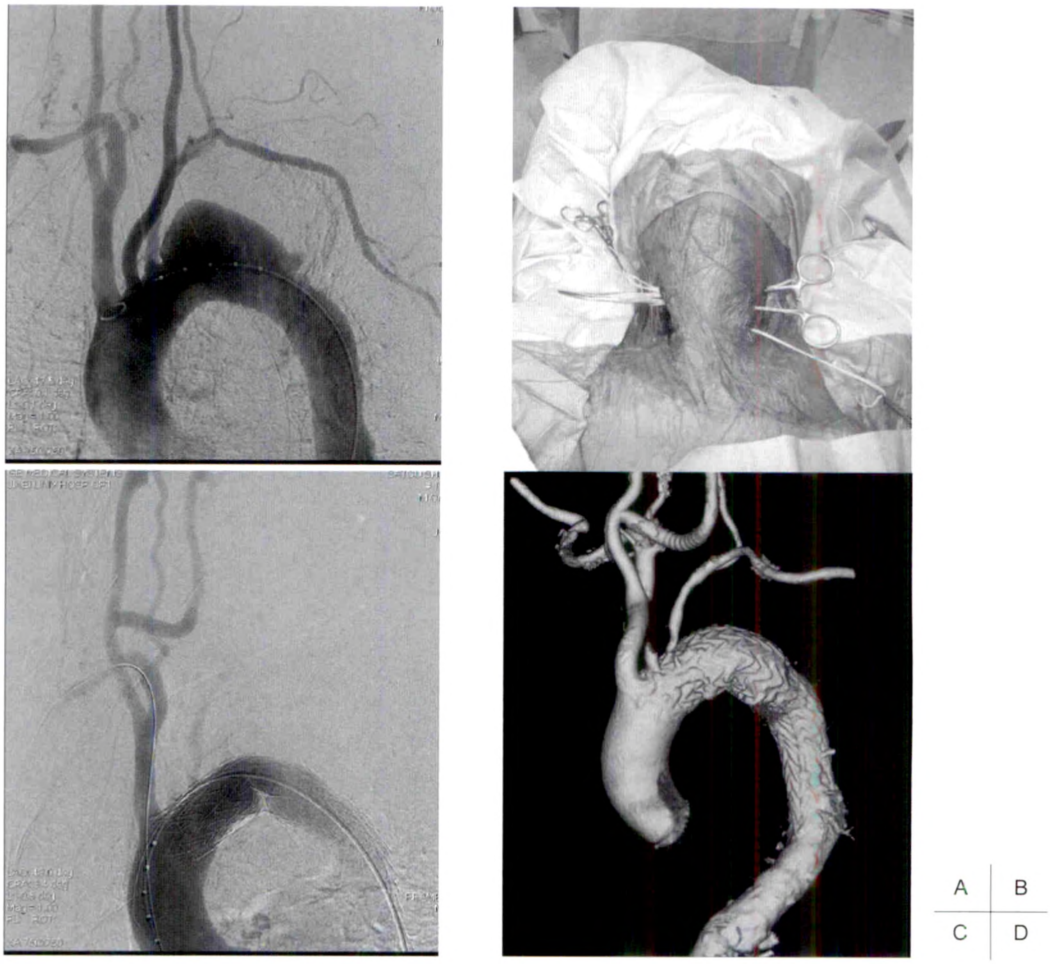

**Fig. 1** TEVAR with partial debranching (carotid-carotid artery cross-over bypass).
**A**: Preoperative angiography shows a distal arch aneurysm located just distal to the left subclavian artery.
**B**: The graft is passed between the esophagus and cervical vertebra.
**C**: Postoperative angiography shows that the aneurysm is excluded from the systemic circulation after partial debranching and TEVAR.
**D**: Postoperative CT angiography reveals that the aneurysm is completely excluded from the systemic circulation.

ascending aorta were necessary for 1 of the 20 cases (5%) and 2 debranching cases (10%), respectively. One case in which the left subclavian artery was covered to apply TEVAR for a distal arch aneurysm was lost due to sudden death from myocardial infarction. Regarding complications, dissection of the ascending aorta occurred in one, and right hemiplegia associated with cerebral infarction occurred in one treated with debranching. In addition, endoleak was noted in 2: a distal arch aneurysm case treated with TEVAR and an arch aneurysm case treated with debranching, and additional stent grafting was necessary after one year.

## DISCUSSION

The TAG stent graft system (W. L. Gore & Associates, Inc.) approved by MHWL as a thoracic stent graft on July 12, 2008 and was made available in Japan (**Fig. 6**). It was approved by the FDA in 2005 and has been widely used in the U.S., and it will also become widely used in Japan. We have been using TAG since 2006, 2 years earlier than the approval by MHWL in Japan. TAG is relatively flexible and bends, readily fitting the curve of the arch, as its characteristics. In addition, it can be accurately placed and is less likely to be moved by blood pressure toward the distally because it is released from the center. Furthermore,

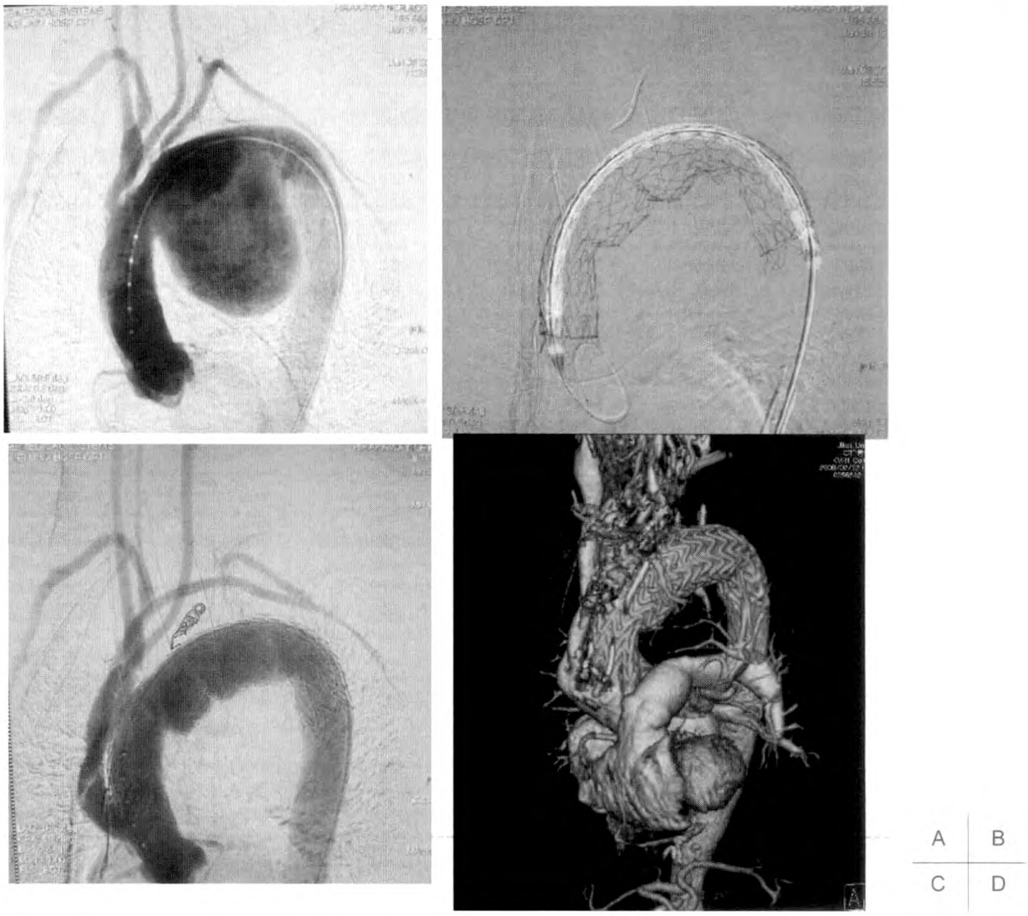

**Fig. 2** TEVAR with total debranching.
**A**: Preoperative angiography shows that neck branches are involved with a huge arch aneurysm.
**B**: The TAG stent graft is deployed from the ascending aorta after total debranching of the neck vessels with a median sternotomy.
**C**: Postoperative angiography shows that the aneurysm is excluded from the systemic circulation after total debranching and TEVAR.
**D**: Postoperative CT angiography reveals that the aneurysm is completely excluded from the systemic circulation.

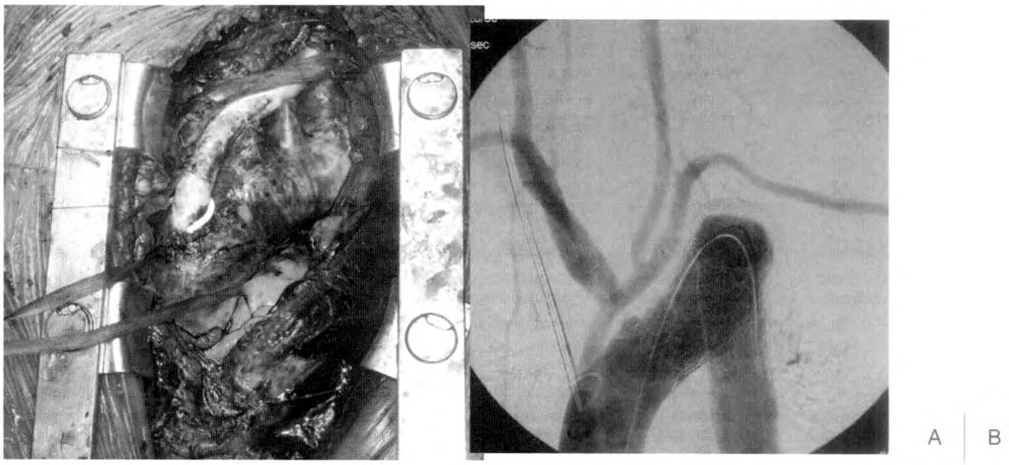

**Fig. 3** Operative view of total debranching + TEVAR.
We usually use the tube graft for debranching the neck vessels.

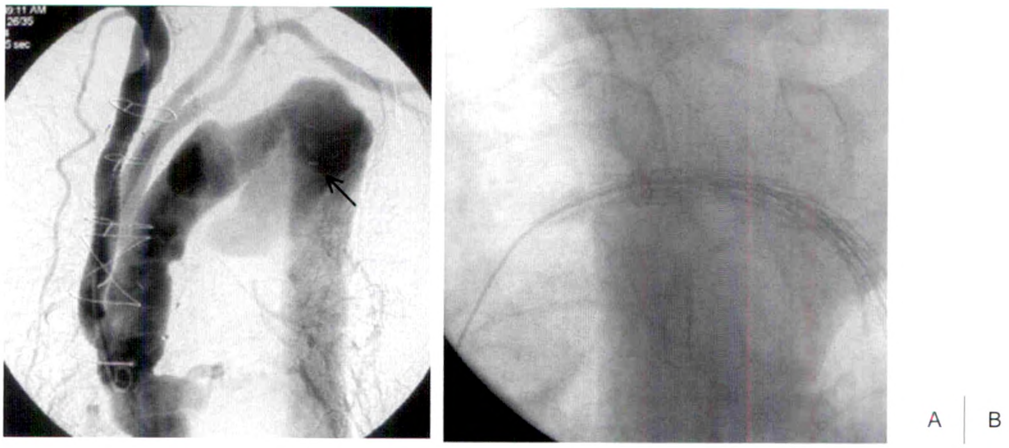

**Fig. 4** Prior total arch replacement with an elephant trunk and TEVAR.
Initial angiography shows a residual thoracic aneurysm after total arch replacement with an elephant trunk. Arrows show the vascular clip to identify the distal end of the elephant trunk.

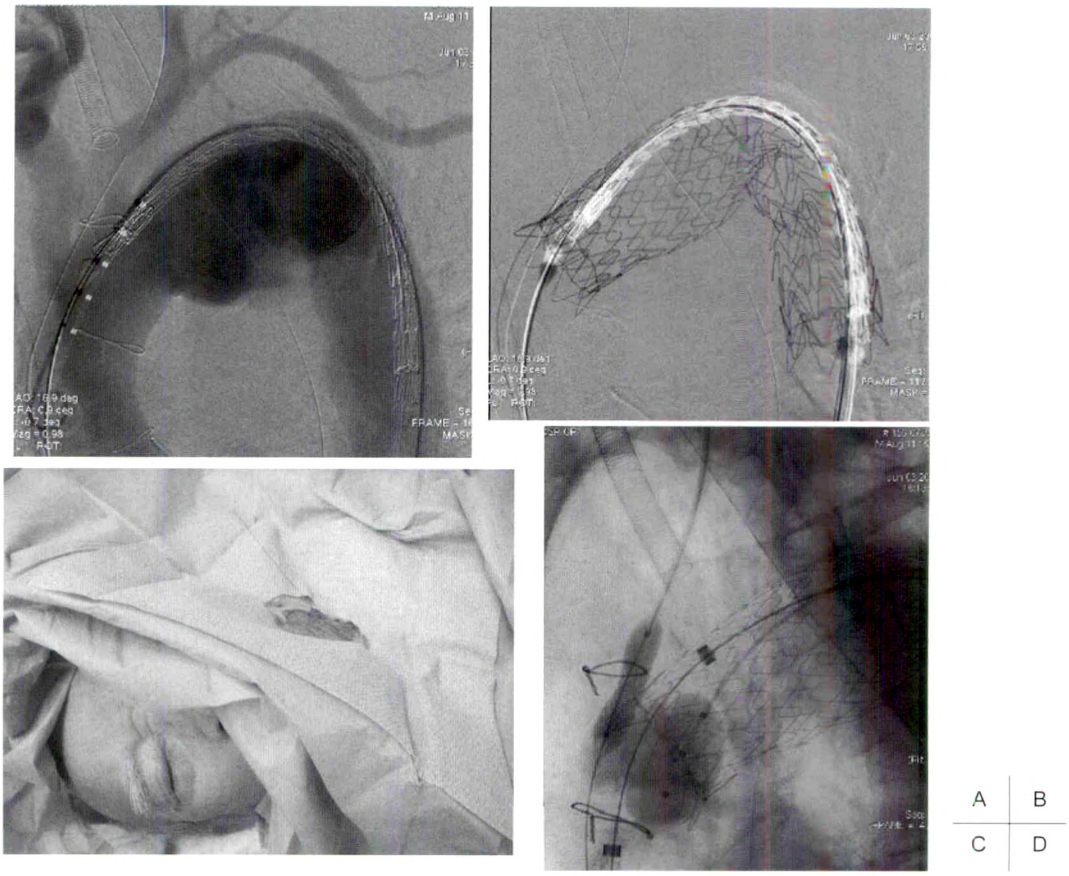

**Fig. 5** TEVAR with carotid puncture wire protection.
A 0.018" guide wire was inserted percutaneously in a retrograde manner through the common carotid artery (CCA) into the ascending aorta with the objective of deploying the stent graft in close proximity to the CCA. When the stent graft is deployed across the CCA, this 0.018" guide wire is used to deliver a balloon-expandable stent in order to restore the patency of the CCA.

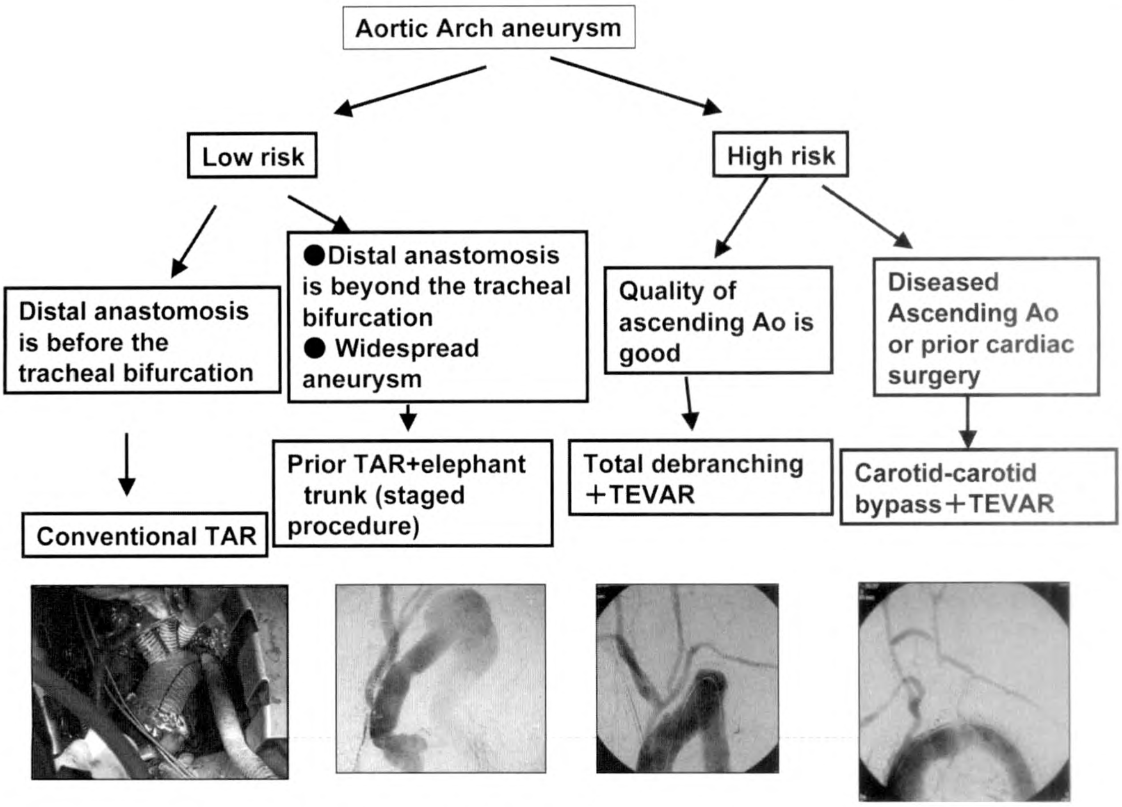
Aortic Arch aneurysm
Low risk
High risk
Distal anastomosis is before the tracheal bifurcation
●Distal anastomosis is beyond the tracheal bifurcation
● Widespread aneurysm
Quality of ascending Ao is good
Diseased Ascending Ao or prior cardiac surgery
Conventional TAR
Prior TAR+elephant trunk (staged procedure)
Total debranching +TEVAR
Carotid-carotid bypass+TEVAR

**Fig. 6** Treatment strategies for aortic arch and distal arch aneurysms.
TAR: total arch replacement

the Tri-lobe balloon for expansion does not completely occupy the aortic lumen when it is inflated, which also avoids moving the stent toward the distally.

The indication is, briefly, aneurysms with a long neck (20 mm or longer) and a diameter of 23–37 mm. According to the clinical trial results of TEVAR using TAG and open repair of thoracic aneurysms in the U.S., the surgical mortality rates were 2.1 and 11.7%, respectively, showing a significantly lower rate in TEVAR.[1)] In addition, the incidence of postoperative complications was also significantly lower in the TEVAR group: spinal ischemia, 14% in open repair vs. 3% in TEVAR; respiratory insufficiency, 20 vs. 4%; renal failure, 13 vs. 1%.[1)] Our outcomes regarding the thoracic descending aortic aneurysms were also favorable. These early outcomes suggested that our treatment plan specifying TEVAR as the first-choice for thoracic aneurysms meeting the anatomical conditions is appropriate.

The delivery sheath size is 20–24 F, which frequently causes problems in peripheral blood vessels including the access route even in western people, and it should be more carefully applied in Japanese with a smaller physique. An unfavorable access route can be dealt with by an iliac arterial approach in many cases.[2–4)] We also investigated the presence or absence of an injury by angiography of the access route while leaving the guide wire after sheath removal, and noted iliac arterial dissection in 8 (12.3%), for which a stent was placed.

The usefulness and low-invasiveness of TEVAR for thoracic descending aneurysms are apparent, but problems of TEVAR are concentrated in arch aneurysms[5,6)]: placement in the curve and maintenance of branch blood flow. To deploy a stent graft in the arch, it is necessary to secure a landing zone as long as possible, for which we devised various methods.

Covering of the left subclavian artery and wire protection (carotid puncture wire protection)

For distal arch aneurysms, covering of the left subclavian artery was necessary to deploy a stent graft in many cases, for which communication between the bilateral vertebral arteries was confirmed on preoperative CT, and the communication was ensured by intraoperative angiography of the vertebral arteries. When the communication is absent, reconstruction of the subclavian artery is considered in cases using the left internal thoracic artery as a graft for coronary artery bypass grafting (CABG). Wire protection is useful to deploy a stent graft directly below the left common carotid artery to elongate the neck, in which the carotid artery is percutaneously punctured using a micropuncture kit, and a 0.018" guide wire is inserted and advanced to the ascending aorta, followed by stent graft deployment (**Fig. 5**).[7,8] This method enables stent graft deployment at the closest proximity of the carotid artery using this wire as a marker, as well as securing antegrade blood flow of the carotid artery by retrograde deployment of a balloon-expandable stent using this wire, as needed. This is a recovery method for the covered carotid artery, giving a sense of security, and it is also useful because the closest proximity of the carotid artery can be targeted. We deployed a stent at the closest site to the left carotid artery in 3 cases, and a stent was placed in the common carotid artery because the left common carotid artery was covered.

## Hybrid surgery

### *1. Carotid-carotid artery bypass (partial debranching)*

This is effective when the aneurysm can be excluded by placing a stent graft at the closest site to the brachiocephalic artery. We make an about 3-cm incision along the anterior margin of the bilateral sternocleidomastoid muscles to expose the common carotid artery, and, normally, an 8-mm PTFE graft is passed along the posterior surface of the esophagus for the shortest distance (**Fig. 1**). In a case using the left internal thoracic artery for CABG and a case with poor communication between the bilateral vertebral arteries, TEVAR was performed after applying bypass to the left subclavian artery. The longest proximal landing zone can be prepared by deploying a stent graft at the closest site to the brachiocephalic artery on combining the wire protection described above, i.e., the following method is useful: 0.018" wire or a 4-F sheath is inserted into the right brachial artery through the exposed right carotid artery, and 0.035" wire is placed in the ascending aorta to deploy a stent graft. Carotid−carotid artery bypass can be safely applied even after heart surgery because no median sternotomy is necessary. On the other hand, a wide landing zone cannot be prepared in cases in which the brachiocephalic and left common carotid arteries are not sufficiently apart or the arteries share a common vessel. Moreover, the proximal side of the stent may be positioned at the arch peak in some cases, to which attention should be paid because the small curvature side rises like a bird beak and may cause endoleak.

### *2. Debranching of all arch branches (total debranching)*

When an aneurysm cannot be excluded unless it reaches t ascending aorta, debranching of all neck branches is useful[9,10] on conditions that the ascending aortic properties are favorable (without calcification and thrombus) and the diameter is 37 mm or smaller. The properties of the ascending aorta are confirmed on preoperative CT, and when the properties are favorable, the ascending aorta is clamped with partial aortic clamps, and the proximal side of a prosthetic graft is end-to-side sutured. We normally end-to-side anastomose the proximal side of an 8-10-mm single prosthetic graft with the ascending aorta, followed by exposure of the brachiocephalic artery and side-to-end anastomosis with the prosthetic graft. The left common carotid artery is similarly side-to-end and the left subclavian artery is end-to-end anastomosed. The proximal sides of the neck branches were closed by suture (**Fig. 2**). The bifurcated prosthetic graft may be used, but, since proximal-side anastomosis was performed under partial clamp, fewer problems occur when the graft diameter is small. Since aneurysms do not disappear, unlike those after arch replacement, a smaller diameter of an additional prosthetic graft is advantageous because the prosthetic graft can be entirely covered with the thymus and fat tissue on closing the sternum. Thus, we use a tube prosthetic graft for reconstruction (**Fig. 3**). After debranching neck branches of an aortic aneurysm, a stent graft is deployed through the femoral artery. We temporary block the prosthetic graftl when TAG is passed through the arch to prevent cerebral infarction. When the access route from the femoral artery is unfavorable, it is useful to deploy a stent graft through one leg of a bifurcated prosthetic graft sutured to the ascending aorta. When the proximal side landing zone is short, we apply banding of the proximal-side neck from outside the aorta or fixation of the stent graft with polypropylene suture applied outside the aorta.

### *3. Two-stage surgery with prior arch replacement (elephant trunk)*

Debranching is not indicated for cases with a dilated ascending aorta. When an aneurysm extends widely, ascending arch replacement precedes to prepare an elephant trunk on the distal side, followed by TEVAR. Setting the proximal-side landing zone in the elephant trunk, a stent graft is deployed in the region ranging to the normal distal region (**Fig. 4**).[11,12] Extended aneurysms can be treated, and this method is also applicable for dissection cases. It is convenient to apply 3-5 vascular clips to the distal end of the elephant trunk during arch replacement as markers for TEVAR.

The open stent method,[13] which has been performed in Japan, is now also used as the frozen elephant trunk technique[14] in western countries. Reportedly, the systemic circulatory arrest can be shortened because distal-side anastomosis in arch replacement can be applied at a more proximal site. This method is indicated for arch replacement with poor properties of the ascending aorta, arch replacement requiring heart surgery, and aortic dissection requiring total arch replacement. However, employment of this method should be carefully decided because the occurrence of paraplegia has been pointed out,[15] and we do not adopt this method.

The indication of TEVAR was expanded by combining surgery for arch and distal arch aneurysms in which a sufficient landing zone cannot be prepared because of the curve and neck branches. When debranching is employed, it is advantageous to perform TEVAR in one stage because temporary clamp of the right common carotid or artery or prosthetic graft during passing a stent graft through the arch may prevent cerebral embolus. However, in the current situation, there is still room for improvement based on the short-term outcomes including the incidence of cerebral infarction; while arch replacement can be performed safely, TEVAR cannot be specified as the first-choice for arch aneurysms. The incidence of endoleak was also higher than that after TEVAR for thoracic descending aortic aneurysms, for which careful follow-up is necessary. At present, we decide on a therapeutic strategy based on the systemic condition and anatomical characteristics of patients (**Fig. 6**).

## CONCLUSION

TEVAR was investigated. The outcome of TEVAR for thoracic descending aortic aneurysms was satisfactory, suggesting that TEVAR is appropriate as a first-choice treatment. In arch and distal arch aneurysms, preparation of a sufficient landing zone is difficult in some cases due to the curve and to maintain blood flow in the neck branches. For these cases, the indication of TEVAR was expanded by combining surgery, but there is still room to improve based on the short-term outcomes. At present, the first-choice treatment for aneurysms involving the arch is arch replacement, and TEVAR should be selected corresponding to cases.

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**Original Article**

# Examination of Difference in the Proximal Anastomotic Site for Crus, Ankle Bypass: Common Femoral Artery vs Below the Knee Popliteal Artery

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***Objective:*** **We evaluated the outcomes of bypass surgery for revascularization in cases of critical limb ischemia with the distal anastomotic site at or below the ankle; we focused on the differences in outcomes between 2 groups having different proximal anastomotic sites.**

***Patients and Methods:*** **Out of 270 cases diagnosed with critical limb ischemia from January 2003 to October 2009, bypass surgeries with the distal anastomotic site at or below the ankle were performed on the limbs of 69 patients (75 limbs). These cases were classified on the basis of the proximal anastomotic sites: group F (n = 50) where the common femoral artery was the proximal anastomotic site and group P (n = 25) where the below-knee popliteal artery was the site.**

***Results:*** **The 5-year cumulative primary/secondary patency rates were 69.3%/81.8% for group F and 68.7%/84.9% for group P. The 5-year cumulative limb salvage rate was 97.9% in group F and 80.3% in group P.**

***Conclusion:*** **Among the cases reviewed, results were comparable between cases with the proximal anastomotic site at the below-knee popliteal artery and those with the site at the common femoral artery.**

***Keywords:*** peripheral arterial disease, critical limb ischemia, femoral to distal bypass, popliteal to distal bypass, peripheral obstructive arterial disease

## INTRODUCTION

Incidence of chronic arterial occlusion disease continues to rise, with increased life expectancy and changing lifestyles. As a result, opportunities to perform surgical lower-limb revascularization procedures like bypass surgeries with the distal anastomotic site in the leg or at or below the ankle are increasing. In this study, we evaluated the outcome of bypass surgery with the distal anastomotic site at or below the ankle; we primarily focused on differences in outcomes between 2 groups having different proximal anastomotic sites.

## SUBJECTS AND METHODS

Of 270 cases of critical limb ischemia diagnosed between January 2003 and October 2009, surgical revascularization was considered feasible and performed in 259 instances. Of these, bypass surgery with the distal anastomotic site in the ankle region was performed on the limbs of 69 patients (75 limbs). These cases were classified on the basis of the proximal anastomotic sites into a femoral artery group (F) and a below-knee popliteal artery group (P). The patency rates for these 2 groups were examined and compared.

Selection of the operative procedure: The proximal anastomotic site was determined using computed tomography angiography (CTA) and duplex scans. In instances

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**Table 1 Patient characteristics**

| | Group F | Group P |
|---|---|---|
| No. of patients/leg (including cases belonging to both groups) | 46/50 | 25/25 |
| Age (mean) | 24–88 (71) | 39–88 (70) |
| Gender (M/F) (including cases belonging to both groups) | 33/13 | 16/9 |
| Disease related with CLI (ASO/TAO) | 43/3 | 24/1 |
| Fontaine grade IIII | 23 (46.0%) | 4 (16.0%) |
| Fontaine grade IV | 27 (54.0%) | 21 (84.0%) |
| DM | 21 (46.7%) | 13 (54.1%) |
| CRF | 12 (26.7%) | 9 (37.5%) |
| MI | 17 (37.7%) | 9 (37.5%) |
| CI | 11 (24.4%) | 6 (25.0%) |

DM: diabetes mellitus; CRF: chronic renal failure; MI: myocardial infarction; CI: cereblovascular infarction; CLI: critical limb ischemia; ASO: arteriosclerosis obliterans; TAO: thromboangitis obliterans

**Table 2 Graft material**

| | No | Group F | Group P |
|---|---|---|---|
| in situ bypass | 26 | 20 (40%) | 6 (24%) |
| Non reversed vein bypass | 18 | 8 (16%) | 10 (40%) |
| Reversed vein bypass | 12 | 4 (8%) | 8 (32%) |
| Spliced vein graft | 19 | 18 (36%) | 1 (4%) |

where no significant lesions were seen in the superficial femoral artery (SFA) as well as the proximal popliteal artery, the below-knee popliteal artery was considered the anastomotic site. The final decision was made by confirming the intraoperative blood flow in the post-anastomotic segment, confirmed beats of the popliteal artery with palpation.

Selection of grafts: Venous autografts were used for every surgery and their properties were evaluated using the duplex scan. The most important factors determining the selection of an operative procedure were the venous properties of each case; where there were no differences in venous properties, the less invasive operative procedure was chosen.

After vascular clamping, 100 U/kg of heparin was intravenously administered. Oral anti-platelet drugs and warfarin were given, and the prothrombin time-international normalized ratio was maintained at 1.5–2.5. After the operation, we started the patients on oral administrations of these drugs. Following surgery, follow-up of the patients was done using duplex scans at intervals of 1 month, 3 months, and every 3 or 4 months thereafter. When suspected stenoses were confirmed, their origins were traced by CTA and additional treatment was provided in cases with significant lesions.

The study included 69 patients (48 men, 21 women) with a mean age of 70 years (range, 24–88 years). A total of 75 limbs were treated. **Table 1** details the preoperative characteristics of the patients and their lesions, including coexisting diseases and the Fontaine and TransAtlantic InterSociety Consensus (TASC) status. **Table 2** provides information regarding the grafts.

The Kaplan–Meier analysis was used to assess primary and secondary graft patency, as well as limb salvage on the basis of the selection of proximal anastomotic sites. Cox hazard testing was used to compare results between the 2 groups. $P$ <0.05 was considered significant. All analyses were conducted using JMP software (version 8.0, SAS Institute, Cary, NC, USA).

## RESULTS

In 1 case of SFA stenting, the proximal anastomotic site determined by the preoperative CTA changed from the below-knee popliteal artery to the common femoral artery on the basis of confirmation of intraoperative blood flow.

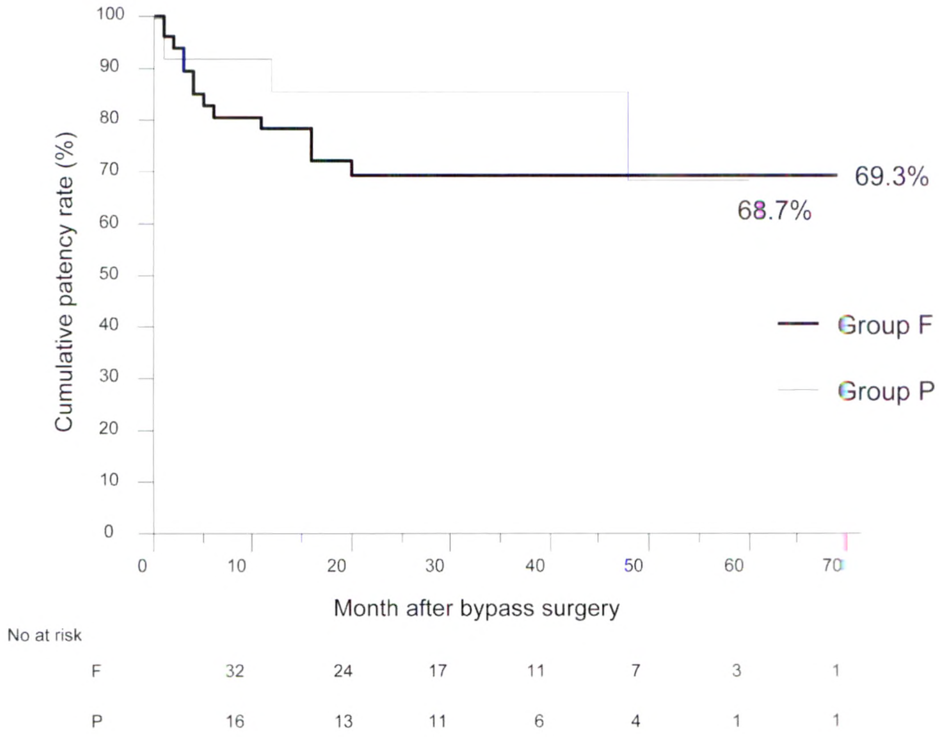

**Fig. 1** Primary patency rates comparing group F to group P. The primary patency rate is 69.3% for group F and 68.7% for group P after bypass surgery.

The mean operative time and the mean blood loss were 298 min and 449.7 ml in group F, and 243 min and 324 ml in group P, respectively.

The 5-year cumulative primary/secondary patency rate was 69.3%/81.8% for group F and 68.7%/84.9% for group P (**Figs. 1** and **2**).

Endovascular repair of SFA was performed simultaneously for 4 group P patients, all of which were TASC A cases who obtained patency during the observation period.

There were no intraoperative deaths; however, occlusion occurred in 11 limbs: 8 (16%) in group F and 3 (12%) in group P. Following occlusion, 8 limbs were Fontaine stage III or below: 6 limbs in group F and 2 limbs in group P. One limb in group F was stage IV, and major amputation from the ankle to the center was performed on 2 limbs (1 limb [2%] in group F and 1 limb [4%] in group P).

In addition, amputation due to infection in spite of graft patency was performed on 3 limbs in group P, all of which were either of patients with diabetes or chronic renal failure. The 5-year cumulative limb salvage rate was 97.9% in group F and 80.3% in group P (**Fig. 3**). There is no statistically significant difference in primary and secondary patency, as well as in the limb salvage rate, between groups F and P.

## Discussion

With an increase in the incidence of diabetes and cases of chronic renal failure,[1] instances of bypass surgery with the distal anastomotic site at or below the ankle have also increased.[2] Securing adequate blood flow at the proximal anastomotic site is fundamental to the bypass procedure. Therefore, in many cases the common femoral artery is chosen as the proximal anastomotic site despite the fact that significant vein harvesting of bypass material is required to cover the entire lower limb. Operative procedures using the popliteal artery site have been reported in Europe and America.[3–7] In Japan, since target lesions of lower limb ischemia localize mostly in the femoral and popliteal arteries, most operative procedures involve the common femoral artery. However, simultaneous to the increase in cases of diabetes and chronic renal failure, situations where lesions in the legs play a main role in the disease pathology have also increased. Due to these changes, the frequency of performing bypass procedures involving the popliteal artery, which was rarely selected

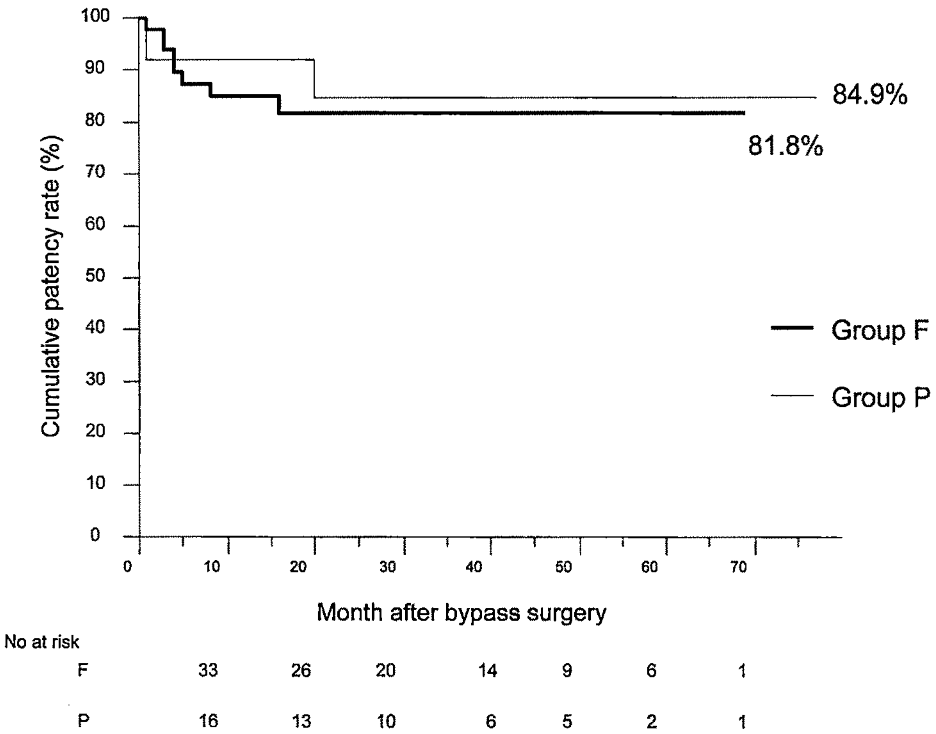

**Fig. 2** Secondary patency rates comparing group F to group P. The secondary patency rate is 81.8% for group F and 84.9% for group P after bypass surgery.

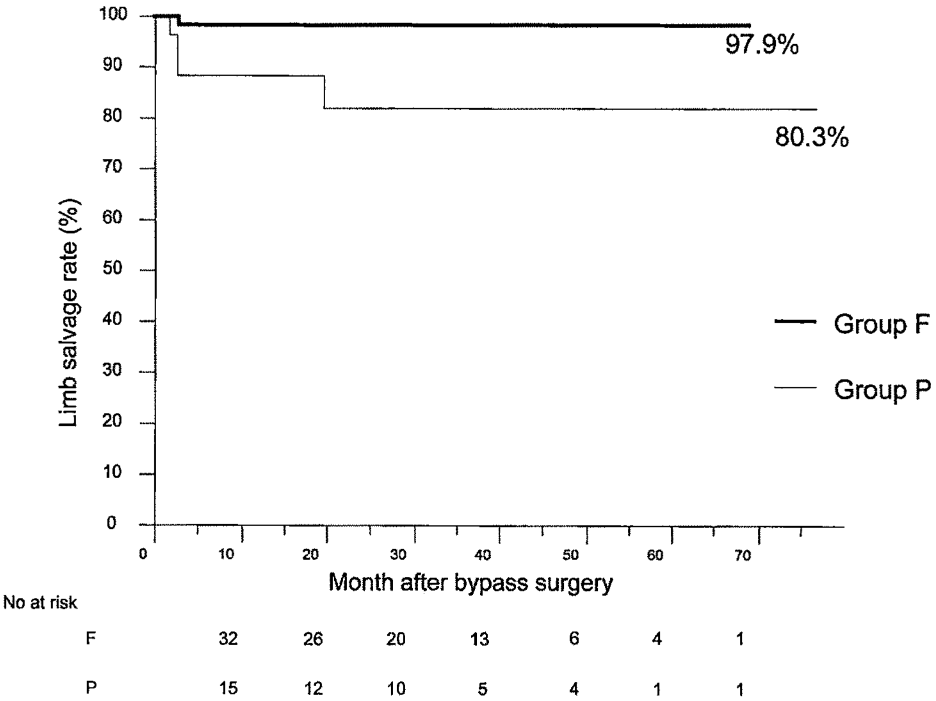

**Fig.3** Limb salvage rates comparing group F to group P. The limb salvage rate is 97.9% for group F and 80.3% for group P after bypass surgery. In addition, amputation due to infection, in spite of graft patency, was performed on 3 limbs in group P, all of which were either of patients with diabetes or chronic renal failure.

before, is increasing.[8)]

The most important factor in the criteria that sets the proximal anastomotic site as the below-knee popliteal artery is the absence of a significant lesion in SFA. Palpable beats of the popliteal artery and absence of significant stenosis on diagnostic imaging were previously reported adaptation conditions.[9)] In the present study, absence of significant lesions on CTA in SFA or the popliteal artery and confirmation of intraoperative blood flow in the below-knee popliteal artery are the adaptation conditions. However, an intraoperative decision taken in 1 case changed the proximal anastomotic site to the common femoral artery. Although, palpable beats of the popliteal artery is somewhat subjective, there is considered reasonable for this study.

Development of lesions in SFA postoperatively is an interesting finding. This phenomenon does not occur very often when the proximal anastomotic site is the below-knee popliteal artery.[10)] Similarly, in our study, significant development of proximal lesions was not seen in the 3 cases with occlusion in group P. Furthermore, no case in group P required additional treatment for proximal SFA lesions during the postoperative observation period. When considering the grafts used, cases with spliced vein grafts totaled 36% in group F, whereas there was only 1 (4%) case in group P. Bypass surgeries in all other cases were performed using a single-vein graft. In addition, in-situ bypasses were also feasible for 24% of group P, a finding similar to that previously reported.[11)] Furthermore, operative time and blood loss tended to be less in group P than in group F. These results support the usage of the below-knee popliteal artery as a proximal anastomotic site, the advantages being a shorter graft length that reduces the amount of vein harvested, simplification of the operative procedure, and reduction in operative time and blood loss. Due to recent developments in endovascular repair procedures, there is an increase in the number of reports on results for TASC A and B lesions in the femoral artery region.[12)] There are also reports on combination endovascular repair for TASC A lesions in the SFA region and bypass surgery in the leg.[13,14)] In this study, endovascular repair was performed in 4 cases of TASC A with similar outcomes. Hence, good results with endovascular repair in the femoral artery region are additional incentives to encourage the use of this bypass design.

Although a previous report had concluded that patency rates are higher when the proximal anastomotic site is at the above-knee popliteal artery than at the below-knee popliteal artery,[15)] the primary and secondary five-year patency rates in our study showed no differences for groups F and P. The results obtained in this study indicate that if neither SFA nor the popliteal artery have significant lesions, the outcome of a bypass surgery using below-knee popliteal artery as the proximal anastomotic site is comparable to that where the common femoral artery is used. Furthermore, there may be an advanced possibility that endovascular repair of SFA to secure inflow may also be established on the basis of strict adaptation.[16)]

## CONCLUSION

Bypass surgery cases around the ankle with the absence of lesions in SFA as well as the popliteal artery, and with the proximal anastomotic site at the below-knee popliteal artery shows results comparable to cases with the site at the common femoral artery.

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**Original Article**

# Lowered Postoperative Ldl-C/Hdl-C Ratio Reduces Later Cardiovascular Events after Abdominal Aortic Aneurysm Surgery

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***Purpose:*** **To examine the relationship between the incidence of later cardiovascular events after abdominal aortic aneurysm (AAA) surgery and postoperative lipid levels.**

***Methods:*** **Atherosclerotic risk factors including postoperative serum lipid levels were examined in 116 patients aged 70 or less undergoing an elective AAA surgery. Later cardiovascular events after AAA surgery occurred in 21 patients, including cerebral infarction (n = 4), catheter intervention or surgery for coronary artery disease (CAD) (n = 10) and other vascular disease.**

***Results:*** **Postoperative cholesterol levels during the average follow-up period of 55.6 ± 44.3 (months) were 49.0 ± 15.7 (mg/dL) for high-density lipoprotein cholesterol (HDL-C), 97.9 ± 31.2 (mg/dL) for low-density lipoprotein cholesterol (LDL-C), which were both significantly improved compared to preoperative values (p <0.001). Cox hazard analysis indicated that preexistent CAD significantly increased in the risk for later cardiovascular events (hazard ratio 5.67; 95%CI 1.92–16.8; p = 0.002) and lowered postoperative LDL-C/HDL-C ratio <1.5 decreased in the risk after AAA surgery (hazard ratio 0.10; 95%CI 0.01–0.83; p = 0.033). Patients with postoperative LDL-C/HDL-C ratio <1.5 (n = 22) had a significantly better cardiovascular event-free rate than those with that ratio ≥1.5 (n = 94) (p = 0.014).**

***Conclusion:*** **Lowered postoperative LDL-C/HDL-C ratio <1.5 can decrease in the risk for later cardiovascular events after AAA surgery. These results may support the rationale for postoperative aggressive lipid-modifying therapy.**

***Keywords:*** abdominal aortic aneurysm, dyslipidemia, cholesterol, lipid-modifying therapy, cardiovascular events

## INTRODUCTION

Abdominal aortic aneurysm (AAA) is an asymptomatic condition with a high mortality rate related to rupture, which has been the cause of 1 to 2% of all deaths in the Western world.[1,2] AAA principally develops from arteriosclerosis, which is often associated with other arteriosclerotic cardiovascular disorders like coronary artery disease (CAD).[1,3–6] The reported mean 5 year crude survival in patients with AAA after surgical repair was approximately 70%, while the expected survival in a control population matched for age and gender was close to 80%.[7,8] The survival was further reduced by about 10% in cases with significant CAD.[8] For the primary

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prevention of atherosclerotic disease, such as CAD, the importance of adequate control of dyslipidemia has been reported, recently, and lipid-modifying therapies like statin treatment have an established role in the treatment of occlusive atherosclerotic disease.[9–11] Although the value of lipid-modifying therapies in the etiology of AAA remains to be controversial, Golledge et al. described the role of high-density lipoprotein cholesterol (HDL-C) levels in predicting the risk of AAA development.[12]

Patients with AAA are at high risk for developing other atherosclerotic cardiovascular disorders, but few reports have described the value of secondary prevention for atherosclerotic disease after AAA surgery.[13] We have previously reported that lowered preoperative HDL-C <35 mg/dL was one of significant predictors for developing later cardiovascular events after AAA surgery.[14] In this previous paper, we conducted detailed investigation on the preoperative characteristics of patients with or without later cardiovascular events.[14] The next point should be the issue as to whether postoperative lipid-modifying therapy can decrease in the risk for later cardiovascular events and improve the prognosis after AAA surgery, even in the high-risk patient group. For that purpose, we retrospectively analyzed the postoperative serum lipid levels and other atherosclerotic risk factors related to cardiovascular events occurrence in patients undergoing AAA surgery. The purpose of this study was to examine the relationship between the incidence of later cardiovascular events after AAA surgery and atherosclerotic risk factors, in particular postoperative serum lipid levels.

## PATIENTS AND METHODS

This retrospective study was performed on 116 patients aged 70 or less undergoing an elective repair of non-ruptured AAA between August 1988 and February 2011 in the Division of Cardiovascular Surgery, Aishin Memorial Hospital. All patients were Japanese and consisted of 108 male and 8 female patients with a mean age of 64.1 ± 5.0 years (range from 50 to 70 years). To limit the influence of aging on cardiovascular events, we limited the patient population in this study to those who were ≤70 years old at the time of surgery. Either preoperatively or postoperatively, 92 patients (79.3%) received treatment for hypertension (HTN); 12 (10.3%) for diabetes mellitus (DM) and 45 (38.8%) received statins for dyslipidemia. There was a history of CAD without an indication for percutaneous catheter intervention (PCI) or coronary artery bypass grafting (CABG) in 35 (30.2%) patients. There were no patients with inflammatory or infectious aneurysm in this study.

The diagnosis of AAA was established by the findings of enhanced computed tomography (CT) in all cases, and AAA greater than 50 mm in diameter were determined to have an indication for surgery. Patients with an indication for AAA surgery received preoperative coronary artery evaluation by traditional coronary angiography (CAG) or coronary CT (CTCAG). A patient was diagnosed as having CAD, when CAG or CTCAG demonstrated stenosis that was equal to or had exceeded 50% (≥50%) in at least one major coronary artery or in its main branch. The treatment option for the CAD, such as PCI or CABG, was determined by the strategy resembling the Guidelines proposed by American College of Cardiology (ACC) and American Heart Association (AHA) Task Force Report in 1993 and its updated version.[15,16] Patients who had a severe CAD with an indication for PCI or CABG at preoperative evaluation or those with perioperative coronary events were excluded from this study. Patients presenting with CAD without an indication for PCI or CABG were defined as having a "known" CAD in this study. The procedure of AAA repair was a prosthetic aortic replacement with a bifurcated or tube graft in all patients, in this study. Patients with a known CAD received perioperative medical treatment with continuous infusion of trinitroglycerin (TNG) at 0.2 to 0.3 μg/kg/min and/or diltiazem (DTZ) at 0.5 to 2.0 μg/kg/min. All smokers were requested to stop smoking before AAA surgery. There were no operative deaths, and the etiologic source of AAA was considered to be atherosclerosis in all patients.

Follow-up of the patient after discharge has been performed periodically in principle at the outpatient clinic in our institute. The mean follow-up period was 55.6 ± 44.3 (months) after AAA surgery. Patients, who were referred to other hospital or lost to follow-up within 3 months after discharge, were excluded from this study. During follow-up at the outpatient clinic, the patient's blood pressure was controlled to a target systolic pressure of less than 140 mmHg and a diastolic pressure of less than 90 mmHg. Patients with HTN received angiotensin-converting enzyme inhibitors or angiotensin-II receptor blockers concurrently with additional oral calcium-channel blockers as appropriate. The β-blockers were selected in those with CAD unless patients presented with bradycardia, chronic obstructive pulmonary disease (COPD), or severe heart failure. The summary of patient profile is shown in **Table 1.**

Cardiovascular events during the follow-up period

**Table 1 Summary of patient profile**

| | | | |
|---|---|---|---|
| The number of patients | 116 | | |
| Age | 64.1 ± 5.0 | | |
| Male/Female | 108/8 | | |
| Follow up period (months) | 55.6 ± 44.3 | | |
| HTN treatment (%) | 92 (79.3%) | | |
| DM treatment (%) | 12 (10.3%) | | |
| Statin treatment (%) | 45 (38.8%) | | |
| Preexistent CAD (%) | 35 (30.2%) | | |
| Cardiovascular events (%) | 21 (18.1%) | | |
| SBP (mmHg) at outpatient | 125.4 ± 18.5 | | |
| DBP (mmHg) at outpatient | 70.6 ± 11.7 | | |
| Preoperative and postoperative lipid levels | | | |
| | preoperative levels | postoperative levels | p value |
| HDL-C (mg/dL) | 39.8 ± 11.6 | 49.0 ± 15.7 | <0.001 |
| LDL-C (mg/dL) | 124.8 ± 29.9 | 97.9 ± 31.2 | <0.001 |
| LDL-C/HDL-C | 3.41 ± 1.22 | 2.47 ± 1.25 | <0.001 |
| TG (mg/dL) | 141.1 ± 70.5 | 100.5 ± 72.9 | 0.028 |

CVE: cardiovascular events; OR: odds ratio; CI: confidence interval; HTN: hypertension; DM: diabetes mellitus; CAD: coronary artery disease; SBP: systolic blood pressure; DBP: diastolic blood pressure; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TG: triglyceride

were defined as the occurrence of cerebral infarction, surgery for other vascular disease, the need for PCI or CABG due to CAD, and deaths from unknown causes. Clinical features including the age and gender, atherosclerotic risk factors, and postoperative lipid levels were recorded and subjected to multivariate analysis to evaluate the rate of freedom from cardiovascular events. The endpoint of this study was defined as the time at cardiovascular events occurrence or time at the end of follow-up for a maximum of 10 years. In patients with multiple cardiovascular events, the time at the first event was defined as the endpoint of the study.

For the measurement of serum lipid levels, blood samples for biochemical assay were in principle collected after an overnight fast, and the serum was separated and analyzed for total cholesterol (TC), HDL-C, and triglycerides (TG) using automated assay. Low-density lipoprotein cholesterol (LDL-C) levels were calculated by Friedewald formula. The LDL-C levels during the follow-up period were in principle controlled with a target value of at least less than 130 mg/dL using lipid-modifying medications including statins (n = 45) and fibrates (n = 17), according to the physician's preference. The data of postoperative lipid levels of each patient were determined by the optimum value (the lowest LDL-C, the highest HDL-C, and the lowest LDL-C/HDL-C ratio) of laboratory data obtained 3 months or later after AAA surgery. This study was approved by the Hospital Ethics Committee, and all patients received a full explanation of surgery and related risks, and postoperative treatment strategy by surgeons.

## Statistical analysis

Continuous variables are presented as the mean ±standard deviation (SD) and compared using the Student's t-test for parametric and Mann-Whitney U-test for nonparametric analyses. Chi-square test was employed for comparisons of nominal valuables. The rate of freedom from cardiovascular events (CVE-free rate) was analyzed by the Kaplan-Meier method and comparisons between the two groups were performed by the log-rank test. The endpoint of each patient for calculating these curves was the day of cardiovascular events occurring or the last follow-up day as described above. A Cox proportional hazard model was applied to determine the effects of valuables on cardiovascular events during the follow-up period. Differences were statistically considered significant at $p < 0.05$. All statistical analysis was performed using Dr. SPSS II version 11.0.1 J (SPSS Inc., Chicago, Illinois).

**Table 2 Relationship between postoperative risk factors and cardiovascular events by Cox proportional hazard analysis**

| | Hazard Ratio | 95% CI | p value |
|---|---|---|---|
| Age | 0.99 | 0.91–1.09 | 0.880 |
| preexistent CAD | 5.67 | 1.92–16.8 | 0.002 |
| HTN | 1.63 | 0.35–7.56 | 0.534 |
| DM | 0.74 | 0.19–2.85 | 0.665 |
| HDL-C >60 | 0.81 | 0.20–3.19 | 0.758 |
| LDL-C <100 | 0.50 | 0.16–1.55 | 0.229 |
| LDL/HDL <1.5 | 0.10 | 0.01–0.83 | 0.033 |
| TG | 1.00 | 0.99–1.01 | 0.416 |

CI: confidence interval; HTN: hypertension; DM: diabetes mellitus; CAD: coronary artery disease; SBP: systolic blood pressure; DBP: diastolic blood pressure; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TG: triglyceride

## RESULTS

Later cardiovascular events occurred in 21 patients, including cerebral infarction (n = 4), catheter intervention (PCI) or surgery for coronary artery disease (CAD) (n = 10), surgery for other vascular diseases (n = 10), and death from unknown cause (n = 1). There were 5 deaths other than cardiovascular events, including deaths from lung cancer (n = 2; at 31 and 102 months after surgery), esophageal cancer (n = 1; 87 months after surgery), pneumonia (n = 1; 91 months after surgery), and head injury (n = 1; 6 months after surgery). The postoperative HDL-C levels (postoperative 49.0 ± 15.7 vs. preoperative 39.8 ± 11.6 (mg/dL)), LDL-C levels (postoperative 97.9 ± 31.2 vs. preoperative 124.8 ± 29.9 (mg/dL)) and LDL-C/HDL-C ratio (postoperative 2.47 ± 1.25 vs. preoperative 3.41 ± 1.22) were all significantly improved compared to preoperative values ($p < 0.001$) (**Table 1**). The postoperative TG levels (100.5 ± 72.9 mg/dL) were also lower than preoperative levels (141.1 ± 70.5 mg/dL) ($p = 0.028$).

Subsequently, clinical factors that may be related to the development of cardiovascular events were assessed with multivariate analysis using Cox proportional hazard model with stepwise method to identify correlations with the later event occurrence. Since the main issue of this study was to examine whether the improvement of postoperative serum lipid levels could reduce the risk for later cardiovascular events, the analysis was, in principal, limited to postoperative serum lipid levels and atherosclerotic risk factors. The items assessed included an age at surgery, a treatment of HTN and DM, preexistent CAD, the postoperative serum HDL-C levels >60 mg/dL, LDL-C levels <100 mg/dL, LDL-C/HDL-C ratio <1.5, and TG levels. The cut-off value of HDL-C, LDL-C, and LDL-C/HDL-C ratio was determined by reference to previous reports[11] and receiver-operating characteristics curves (ROC curves) using statistical software.

The results are shown in **Table 2.** Cox hazard analysis indicated that the preexistence of CAD significantly increased in the risk for later cardiovascular events (hazard ratio 5.67; 95%CI 1.92–16.8; $p = 0.002$) and the lowering of postoperative LDL-C/HDL-C ratio <1.5 decreased in the risk after AAA surgery (hazard ratio 0.10; 95%CI 0.01–0.83; $p = 0.033$). In contrast, the increase in postoperative serum HDL-C levels >60 mg/dL (hazard ratio 0.81; $p = 0.758$), decrease in postoperative serum LDL-C levels <100 mg/dL (hazard ratio 0.50; $p = 0.229$) did not significantly reduce the risk for later cardiovascular events.

According to the relationship between the postoperative LDL-C/HDL-C ratio and cardiovascular events occurrence, we divided the 116 patients, examined in this study, into the following two groups to compare clinical features: 1) those with postoperative LDL-C/HDL-C ratio <1.5 (Low ratio group: n = 22); 2) those with postoperative LDL-C/HDL-C ratio ≥1.5 (High ratio group: n = 94). In univariate analysis of clinical factors, there were no significant differences in the age, gender, systolic and diastolic blood pressure at the outpatient clinic, incidence of a treatment of DM, and statin treatment between the two groups (**Table 3**). A treatment of HTN was more common among the Low ratio group than the High ratio group ($p = 0.006$) and the prevalence of CAD tended to be higher in the High ratio group than in the Low ratio group

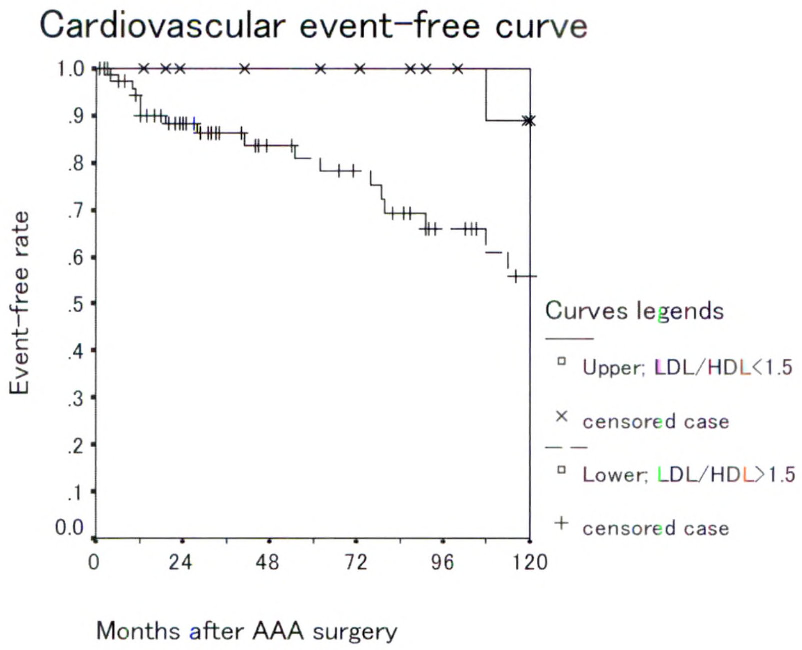

**Fig. 1** Kaplan-Meier curves indicating freedom from cardiovascular events in the group of patients who exhibited the ratio of LDL-C/HDL-C <1.5 and those who did not. LDL-C: low-density lipoprotein; HDL-C: high-density lipoprotein

**Table 3 Comparative studies of clinical features between the two groups**

| | LDL-C/HDL-C <1.5 (Group A; n=22) | LDL-C/HDL-C ≥1.5 (Group B; n=94) | p value |
|---|---|---|---|
| Age | 63.6 ± 5.3 | 64.2 ± 5.0 | 0.609 |
| Male/Female | 19/3 | 89/5 | 0.174 |
| HTN treatment (%) | 22 (100%) | 70 (74.5%) | 0.006 |
| DM treatment (%) | 4 (18.2%) | 8 (8.5%) | 0.237 |
| Statin treatment (%) | 10 (45.5%) | 35 (37.2%) | 0.476 |
| preexistent CAD (%) | 3 (13.6%) | 32 (34.0%) | 0.073 |
| Cardiovascular events (%) | 1 (4.5%) | 20 (21.3%) | 0.067 |
| SBP (mmHg) at outpatient | 125.6 ± 26.9 | 125.4 ± 16.2 | 0.978 |
| DBP (mmHg) at outpatient | 74.4 ± 16.2 | 69.7 ± 10.4 | 0.252 |
| pre HDL-C (mg/dL) | 43.6 ± 12.8 | 38.8 ± 11.2 | 0.119 |
| pre LDL-C (mg/dL) | 119.1 ± 35.5 | 126.9 ± 28.1 | 0.367 |
| pre LDL-C/HDL-C | 3.00 ± 1.30 | 3.52 ± 1.19 | 0.117 |
| pre TG (mg/dL) | 124.7 ± 83.8 | 144.9 ± 67.1 | 0.238 |
| post HDL-C (mg/dL) | 63.7 ± 17.9 | 45.5 ± 13.0 | 0.095 |
| post LDL-C (mg/dL) | 66.9 ± 24.8 | 105.2 ± 28.1 | <0.001 |
| post LDL-C/HDL-C | 1.14 ± 0.26 | 2.78 ± 1.19 | <0.001 |
| post TG (mg/dL) | 81.9 ± 39.2 | 105.1 ± 77.0 | 0.175 |
| Follow up period (months) | 81.3 ± 41.7 | 49.6 ± 42.9 | 0.003 |

CVE: cardiovascular events; OR: odds ratio; CI: confidence interval; HTN: hypertension; DM: diabetes mellitus; CAD: coronary artery disease; SBP: systolic blood pressure; DBP: diastolic blood pressure; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TG: triglyceride; pre: preoperative; post: postoperative

(p = 0.073). Difference in the preoperative lipid levels between the two groups did not reach statistical significance, but the postoperative LDL-C levels in the Low ratio group were significantly lower than those in the High ratio group (p <0.001) and postoperative HDL-C levels in the Low ratio group tended to be higher than those in the High ratio group (p = 0.095). The mean follow-up period was 81.3 ± 41.7 (range 13 to 120) months for the Low ratio group, which was significantly higher than those for the High ratio group (49.6 ± 42.9 (range 3 to 120) months) (p = 0.003). The difference in the follow-up period between the two groups may result from the difference in the prevalence of cardiovascular events occurrence, which was the endpoint of this study.

**Figure 1** shows a comparison of Kaplan-Meier curves indicating the rate of freedom from cardiovascular events between the two patient groups divided based on the postoperative LDL-C/HDL-C ratio. As shown in the **Fig. 1**, there was a significant difference in the freedom from cardiovascular events depending on the postoperative LDL-C/HDL-C ratio. Patients with postoperative LDL-C/HDL-C ratio<1.5 had a significantly better cardiovascular event-free rate than those with LDL-C/HDL-C ratio ≥1.5 (p = 0.014 by the log-rank test).

Regarding the relationship between statin treatment and later occurrence of cardiovascular events; the events occurred in 13 of 45 patients (28.9%) who had received statin treatment, whereas, they occurred in only 8 of 71 patients (11.3%) who had not received the treatment. The occurrence of cardiovascular events depended much on the LDL-C/HDL-C ratio as described above, rather than on the presence or absence of statin treatment in our study.

## DISCUSSION

In the previous literature, the 5 year crude survival rate in patients having undergone AAA repair was reported to be about 70%, which was less than the expected survival of 80% in a matched population.[7,8] In patients with AAA, comorbidity of HTN, dyslipidemia, COPD, CAD and other cardiovascular diseases are frequently found prior to surgery, most of which are also determinants of long-term survival after AAA surgery.[17,18] The reported risk factors affecting long-term survival included an increasing age, presence of heart disease, HTN, COPD, renal insufficiency, and continuing smoking.[7,19] Of these, cerebral and cardiovascular diseases are responsible for approximately two-thirds of late deaths, thus appropriate management of these conditions would be essential to ameliorating long-term survival.[17–22]

The importance of adequate control of dyslipidemia has been emphasized recently for the primary prevention of atherosclerotic disease,[9–11] but the evidence for the role of lipids in the development and management of AAA remains to be controversial. Some recent reports, however, described the significant association between lipid levels and AAA. Hobbs et al. reported a highly significant association between LDL-C and small AAA, and LDL-C was thought to be an initiating factor in the development of an AAA.[23] Golledge et al. indicated that HDL-C appeared to be the most important lipid in predicting the risk of AAA development.[12] Preoperative HDL-C levels are also one of significant predictors for developing later cardiovascular events after AAA surgery in our previous report.[14] Therapeutic approaches to dyslipidemia like those in the treatment of CAD may be beneficial for the secondary prevention of atherosclerotic disease after AAA surgery.

Since an increasing age is consistently identified as a strong risk factor for atherosclerotic disease like AAA,[1] the age distribution of the study group may have a significant influence on the results from the study like this investigation. For example, the Tromso study included a very wide range of ages (25 to 82 years), thus, the results may not reflect the true risk factors because the risk period for the development of an AAA did not occur for many patients aged <50 years.[1] To minimize the influence of aging on the later events during the follow-up period, the subjects in this study were limited to those aged 70 or less at surgery.

In the analyses of lipid levels, in all cases, the postoperative HDL-C, LDL-C, and LDL-C/HDL-C ratio were all significantly improved compared to preoperative values (p <0.001). This was probably due to postoperative management of atherosclerotic risk factors including statin treatment, although aggressive lipid-modifying medications were not always given to patients during the follow-up period. Lifestyle guidance such as diet and exercise therapy has been intensively conducted by medical personnel in the outpatient clinic throughout the follow-up period, which may have contributed to the improvement of lipid levels. The reason for the higher incidence of HTN among the Low ratio group (patients with LDL-C/HDL-C ratio <1.5) than the High ratio group was not clear, but those with HTN who visited the hospital, regularly, might have good adherence to the lifestyle guidance.

Cox proportional hazard analysis indicated that the preexistence of CAD significantly increased the risk for later cardiovascular events (hazard ratio 5.67; $p = 0.002$) and the lowering of postoperative LDL-C/HDL-C ratio <1.5 decreased in its risk after AAA surgery (hazard ratio 0.10; $p = 0.033$). Isolated postoperative LDL-C and HDL-C values per se were not identified as predictors for later cardiovascular events. Presence of CAD has been reported to be a strong predictor of the late survival after AAA surgery,[7,8,21] which is well consistent with the current study results. In our previous report, further decrease in the preoperative HDL-C levels increases in the risk for cardiovascular events after AAA surgery.[14] There was about a three-fold higher risk for the development of cardiovascular events in those with the preoperative HDL-C levels <35 mg/dL. Preoperative LDL-C/HDL-C ratio was also predictive, but the value was less than simple HDL-C levels.[14] HDL-C has been reported to oppose atherosclerosis by removing cholesterol from foam cells, by inhibiting the oxidation of LDL-C, and by limiting the inflammatory processes that underlie atherosclerosis.[9]

In the analyses of postoperative lipid levels, in this study, we investigated an LDL-C/HDL-C ratio as an important marker, in addition to LDL-C and HDL-C levels. In guidelines for cardiovascular disease risk management, LDL-C is the principal target of lipid-lowering therapy; however, recent evidence has suggested more appropriate targets, including non HDL-C, apolipoprotein B, and ratios of total/HDL-C, LDL-C/HDL-C.[11,24] The ratio of LDL-C/HDL-C reflects both lipid levels of LDL-C and HDL-C, and it has been reported that lowering the ratio by lipid-lowering therapy is associated with a lower incidence of cardiovascular events in the setting of primary prevention.[11] Current study also indicated that the lowering of postoperative LDL-C/HDL-C ratio <1.5 decreased in the risk for later cardiovascular events. In addition, patients with postoperative LDL-C/HDL-C ratio<1.5 had a significantly better cardiovascular event-free rate than those with that ratio ≥1.5 ($p = 0.014$). These results could be consistent with findings from previous reports.[11]

In the analyses of atherosclerotic risk factors and postoperative lipid levels between the two groups divided, based on the LDL-C/HDL-C ratio shown in **Table 3**, the difference in the preoperative lipid levels between the two groups did not reach statistical significance. The postoperative LDL-C levels in the Low ratio group were, however, significantly lower than those in the High ratio group ($p < 0.001$) and postoperative HDL-C levels in the Low ratio group tended to be higher than those in the High ratio group. These results may suggest that risk for later cardiovascular events could be reduced even in patients with low preoperative HDL-C levels, i.e., those at high risk for later cardiovascular events. Preoperative HDL-C level is indeed a strong predictor for later cardiovascular events as shown in the previous report,[14] but the high risk could be modified depending on postoperative management. For that purpose, intensive control of lipid levels would be necessary that can achieve the lowered LDL-C/HDL-C ratio as low as less than 1.5.

These results indicate that the ratio of LDL-C/HDL-C could be employed as a beneficial index during the follow-up for patients having undergone AAA repair, aiming at a target value of LDL-C/HDL-C ratio less than 1.5. The introduction of endovascular repair (EVAR) was associated with an increasing incidence of intact AAA repair and improvement in operative mortality; a greater number of patients with AAA may receive postoperative long-term follow-up.[25] Since cerebral and cardiovascular diseases are responsible for approximately two-thirds of late deaths in patients receiving AAA repair, decrease in the cardiovascular events by adequate control of lipid levels may contribute to improvement of prognosis and late survival in these patients.[17–22]

Regarding the relationship between the statin treatment and later cardiovascular events occurrence, the statin treatment itself did not reduce the prevalence of later cardiovascular events in this study. As statins would be given to those with dyslipidemia exhibiting a high serum level of LDL-C or low level of HDL-C, there would be many patients at high risk for developing cardiovascular events in the patient group receiving statins. Development of side effects by statins may vary from patient to patient; thus, an adequate lipid level may not be obtained in patients who developed some side effects like myalgia or liver dysfunction. Cardiovascular events occurrence depended much on whether adequate lipid levels were obtained or not, rather than the presence or absence of statin treatment in our study. Probably, aggressive lipid-modifying therapy, including drug, diet, and exercise therapy, aiming at a clearly targeted value of LDL-C/HDL-C ratio would be necessary to reduce the incidence of cardiovascular events occurrence.

There are some limitations in this study. In our study design, patients with AAA were retrospectively examined and divided into the two groups based on the postoperative LDL-C/HDL-C ratio, as a single center experience. Lipid-modifying therapy was not given to all patients after surgery based on the condition of patients. Ideally, a randomized prospective study is required to determine the value of predictor with a larger number of patients. Second, the findings of our study were limited to those aged <70 at surgery, thus, the value of LDL-C/HDL-C ratio in patients with age older than the present study group is unknown. Since the majority of subjects were male patients, we can draw no conclusions on the association of lipids with cardiovascular events in women. Third, the follow-up period is relatively short in some patients, thus, the short follow-up period may influence on the incidence of cardiovascular events. Although there are many limitations, our study results may help to understand the predictive value of serum lipid levels and to prognosticate the outcome at least in part of patients with AAA.

In conclusion, our study indicated that lowered postoperative LDL-C/HDL-C ratio <1.5 can decrease in the risk for later cardiovascular events after AAA surgery. These results may support the rationale for postoperative aggressive lipid-modifying therapy in patients undergoing AAA repair.

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**Original Article**

# Clinical Study of Phlebitis Migrans and Incompetence of the Leg's Superficial Vein in Buerger Disease

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**Three of four (75%) vein biopsy samples from four patients (all male, mean onset: age 33.0, mean biopsy: age 59.7) of chronic phase phlebitis migrans showed positive periodontal bacteria DNA under the PCR (polymerase chain reaction) method.**

**Of the 24 cases of Buerger disease (22 males, 2 females, mean onset: age 31.9, mean examination: age 62.6) that were investigated in our vascular laboratory, 65% of the patients suffered from moderate to severe varicose veins. Eight cases had a history of phlebitis migrans and three had an active ulcer or uncontrollable erosion in the foot. The rate of incidence was significantly higher than that of the well-matched control group. Other findings included one instance of deep vein thrombosis, and one instance of deep vein reflux.**

**We could suggest that some intractable ulcer or erosion cases of Buerger disease may be complicated by superficial vein incompetence or other deep vein insufficiency. We also we need to check Buerger disease patients with duplex for vein reflux and other insufficiencies. Treatment of the varicose veins (including elastic stockings) was effective for all of the patients. (English Translation of Jpn J Phlebology 2011; 22: 25–31.)**

*Keywords:* phlebitis migrans, buerger disease, foot ulcer, superficial vein incompetence, varix surgery

## INTRODUCTION

In the early 1900s, Leo Buerger emphasized the presence of phlebitis migrans in Buerger disease in addition to arterial lesions.1) The phlebitis is defined as a characteristic finding for the diagnosis of Buerger disease. However, the long term results of the phlebitis or duplex examination of the superficial or deep vein have not been reported.2) In addition, it is not recognized that some of the chronic ulcers came from incompetence of the venous system.

## MATERIALS AND METHODS

1) PCR (polymerase chain reaction) Study: Four samples of the pigmentation portion of the phlebitis migrans or relatively fresh phlebitic vein near the ulcer were collected from four patients. A well-established PCR method was carried out for periodontal bacterial DNA. The patients were all male, and the onset age was 33.0 years. Symptoms and conditions included major amputation (2 cases), post-arterial reconstruction (1 case), and ischemic ulcer (1 case). The mean age at harvest was 59.7 years. The same examination was performed on the

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**Table 1 Results of periodontal examination and PCR detection of phlebitis migrans in patients with Buerger disease**

| Age | Sex | Onset age | Main condition | Sample sites | Oral cavity bacteria | Vein bacteria |
|---|---|---|---|---|---|---|
| 53 | M | 32 | BK | foot | Pg, Tf, Td, Pn | Pg, Td |
| 62 | M | 34 | AK | thigh | Pg, Tf, Td, Cr, Pi | Pg, Td, Cr, Pi |
| 59 | M | 41 | bypass | foot | Pg, Tf, Td, Cr, Pi | none |
| 65 | M | 25 | ulcer | leg | Pg, Tf, Td, Cr, Pi | Cr |

All patients adapted on Shionoya's criteria for Buerger's disease.[3)]

PCR: polimerase chain reaction; Pg: Porphyromanas gingivalis; Tf: Tannerella forsythus; Td: Treponema denticola; Cr: Campylobacter rectus; Pi: Prevotella intermedia; Pn: Prevotella nigrescens; BK: below knee amputation; AK: above knee amputation; lt: light; rt: right

oral saliva. The diagnosis was defined using Shionoya's criteria.[3)]

2) Duplex Study: About 24 Buerger disease patients (mean age 62.6 years, range of ages was 29–76, male/female ratio: 22/2, and onset average age of 31.9 years) were studied. We checked pigmentation along the lower limbs' superficial veins, ulcers, or erosion, and the presence of the valve incompetence and the deep vein thrombosis.

We utilized a colored duplex device (XarioXG Toshiba Medical Systems) in the inspection and searched for the presence of reflux of the great and small saphenous vein, the vein diameter, the presence of the main incompetent perforating vein, and the presence of deep vein thrombosis in a standing position. The diagnosis was equal to a Study 1) using Shionoya's criteria.

As a control, 58 males (average age 64 ± 10 years) were randomly selected and examined for the frequency of the varicosity using the above-mentioned methods.

## RESULTS

1) Oral bacteria DNA in 3 of 4 examples was detected (75%). All presented with bacteria in the oral cavity. We detected four kinds of bacteria; Pg (Porphyromanas gingivalis), Td (Treponema dentiocola), Cr (Campylobacter) and Pi (Prevotella intermedia). In two cases, Pg, Td, and Cr were all present. Pi was present in one case. From the oral cavity, other periodontal bacteria were identified as well as the above-mentioned bacteria. Refer to **Table 1** for details.

2) Eight patients (33.3%) had pigmentation of a leg or a foot and were judged to have a history of phlebitis migrans. An ulcer, or erosion, was observed in three cases. There was no acute phlebitis case that was accompanied by redness or pain.

Reflux in a branch or a saphenous vein trunk was observed in 15 cases by ultrasonic investigation in the standing position (62.5%). Other studies showed deep vein reflux in one case and deep vein thrombosis in one case (the patient underwent varicosity surgery in another hospital). A quick glance reveals that there was little meandering varicosity except in two limbs among the incompetent veins.

Subjects with significant reflux of the saphenous veins wore elastic stockings and vein ligation and/or sclerotherapy was performed on the subjects with an ulcer or erosion. All were healed.

In about 58 control normal males (average age 64 ± 10 years), the lower limbs varicosity rate was 22% (13/58). No deep vein thrombosis, deep vein reflux, or perforated vein incompetence were observed.

There was a significantly lower limb varicosity rate in comparison with the Buerger disease patients ($p < 0.01$, Z test $Z = 3.86$).

*Case 1*

59 year-old male. Chief complaint: ulcer of left dorsum of the foot.

His first symptoms, a pale and fatigued foot, appeared at the age of 22. It was diagnosed as Buerger disease when he was 25 years old.

He underwent various treatments before receiving a left lumbar sympathectomy at age 29. He smoked over 20 cigarettes per day from age 20 to 35 and then gave up smoking.

He observed pigmentation and phlebitis like changes on both sides of the foot and leg from about age 45. His chief complaint was of left foot ulcers for 12 years, which became intractable. The ulcer is 4 × 6 cm wide and 1 cm deep (**Fig. 1**). He lost eight teeth and had dentures made. During the time that he smoked, he had gingivitis.

The angiography showed that three below-the-knee vessels that are occluded in the left and peroneal artery have been replaced with corkscrew-type collateral.

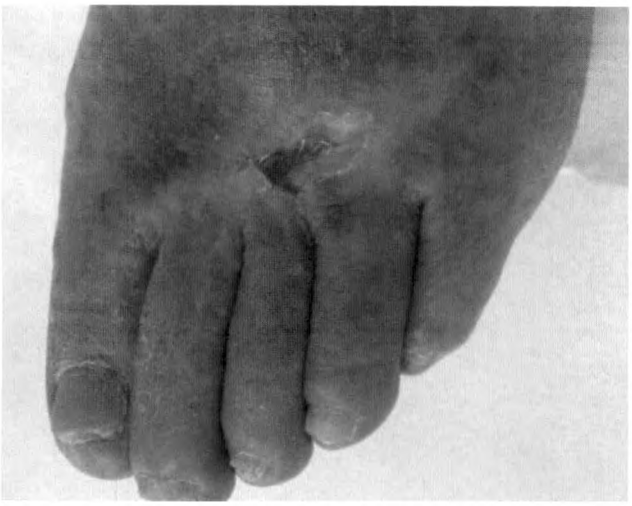

**Fig. 1** A 59 year-old male complaining of ulcer on the dorsum of the left foot for 12 years. Skin pigmentation is remarkable. Photo taken in 2006.

In the right leg, posterior and anterior tibial arteries are occluded at the origin, and the peroneal artery is occluded at the ankle joint (**Fig. 2a**). The right and left ulnar arteries are occluded according to the Allen test. He has no diabetes, hyperlipidemia, or hypertension. The ABI is 1.38 on the right, and 0.73 on the left.

The color duplex findings on the right side reveal great and small saphenous vein reflux for the full length and in the left accessory, great saphenous vein reflux was demonstrated. The deep veins were normal (**Fig. 2b**).

The ulcer was reduced with the use of an elastic bandage and elastic stockings after the first examination by the vascular surgeon in April 2006. By August, the reflux had disappeared due to the combination of the great saphenous vein ligatures and sclerotherapy. The ulcer healed in September 2006 (**Fig. 3**). In 2007, he resumed hiking, his favorite activity, and continued to recover. He later was able to ski.

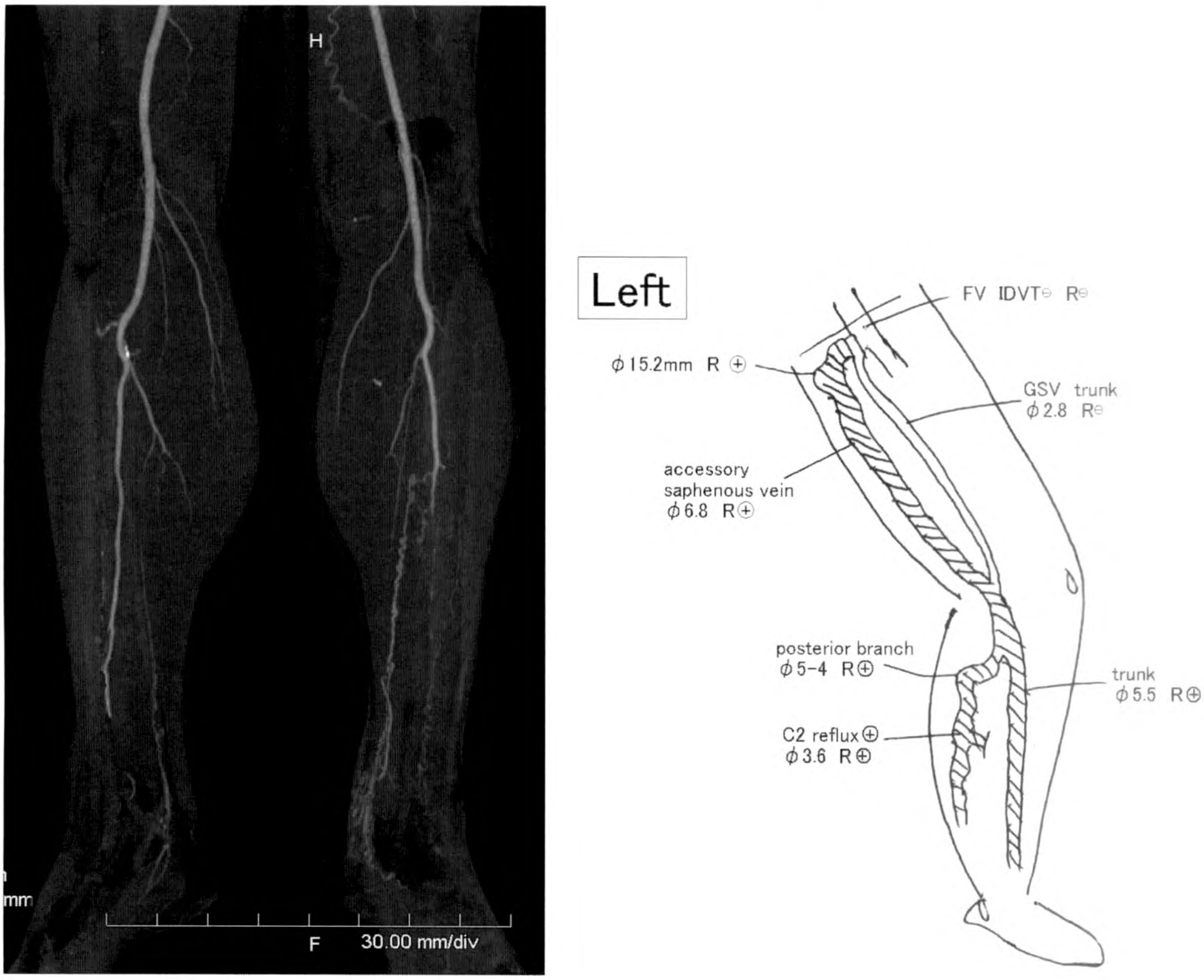

**Fig. 2**

**a**: Angiographyof the case showing typical Buerger disease.

**b**: Venous echogram showing reflux of the great saphenous vein.

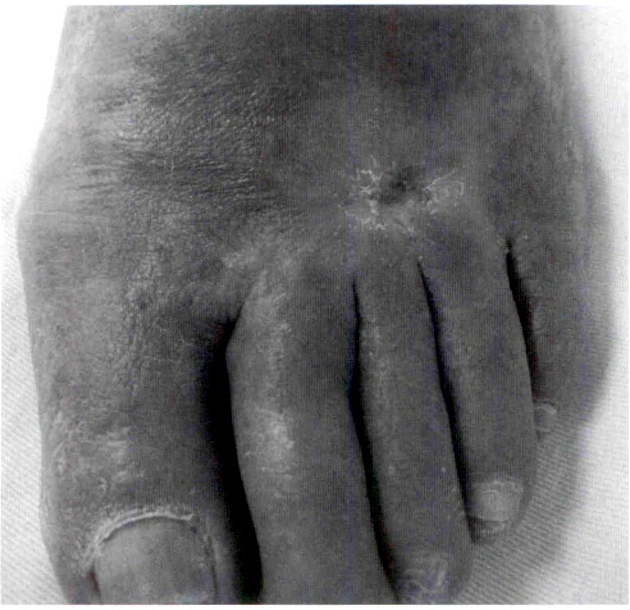

**Fig. 3** Photo one month after saphenous vein ligation and sclerotherapy. The ulcer healed rapidly.

### Lower limbs vein studies in three young Buerger disease patients (under age 55)

*Case 2–1*

A 29 year-old male diagnosed with Buerger disease at age 23. He smoked 80 cigarettes per day for five years. His chief complaint was intermittent claudication (100m).The ABI is 0.48 on the left, and the right is normal. The left superficial artery was occluded at the Hunter canal and the anterior tibial artery was occluded at the foot level. The duplex study showed left-side great saphenous vein reflux for almost the entire length and the saphenofemoral junction was 10.5 mm in diameter (**Fig. 4**). It rose to ABI0.79 with the use of elastic stockings and a 2 year ban on smoking from July 2010. He is on an anti-platelet agent. He had gingival bleeding while he smoked, but there was no damage to his teeth.

*Case2-2*

A 43 year-old male who developed Buerger disease, it is at age 28. He was a pack-a-day smoker for 10 years. His few symptoms stabilized after he stopped smoking in 2008. The ABI was in the normal range. As for the lower limb arteries, there is bilateral posterior tibial artery occlusion and anterior tibial artery narrowing with occlusion of the foot arteries.

The left ulnar artery is occluded. The trunk of the great and small saphenous veins showed no reflux, but a superficial branch vein revealed reflux. He can walk in the treadmill test for five minutes, but there is a feeling of wrongness in the big toe. He takes no medicine for the condition.

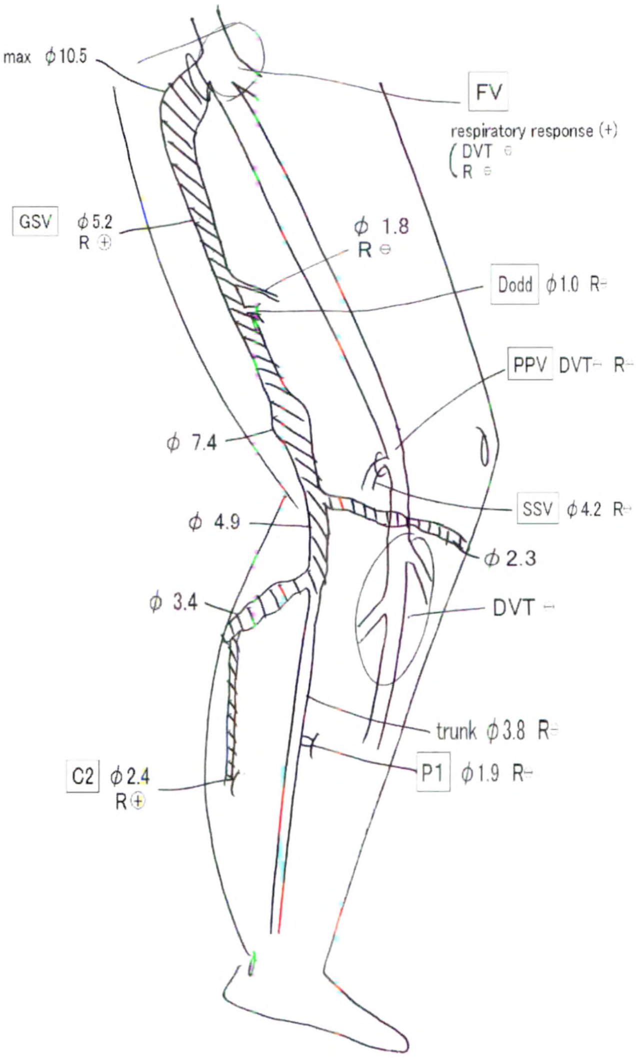

**Fig. 4** A 29 year-old male. Arteriogram revealed typical Buerger disease and venous echogram showed severe reflux of great saphenous vein.

*Case 2–3*

A 55 years old male who developed Buerger disease, it is at age 23. He had a left below-the-knee amputation and amputations of the right big toe and third toe afterward. An angiography showed femoral and popliteal artery occlusion on the left and on the right, anterior tibial artery occlusion, and narrowing of the posterior tibial artery. He has few surviving healthy teeth in his lower and upper jaws (**Fig. 5**). There was right leg pigmentation and a 3 × 4 cm ulcer/erosion in the medial foot, and erosions

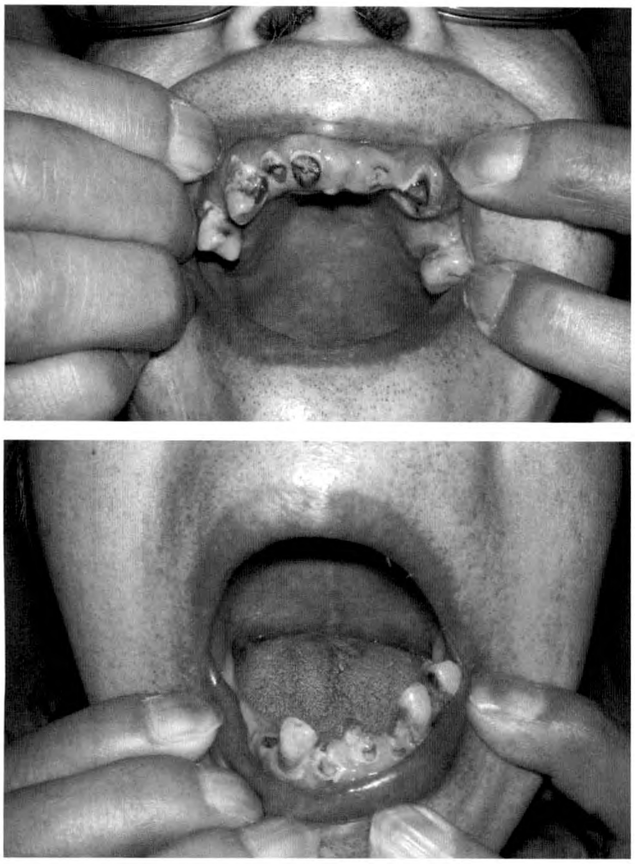

**Fig. 5** A 55 year-old male showing severe dental condition since age 23 when his symptoms started. Venous reflux demonstrated in the great and short saphenous veins with wide wet erosion which healed quickly after venous ligation and sclerotherapy were performed.

between the second and third toe and the fourth and fifth toe. The duplex study showed reflux in the great and small saphenous veins. Saphenous vein ligations and sclerotherapy were performed in December 2009. The result was good, and the ulcer and erosion healed in January 2010. He is receiving oral care from a periodontal dentist.

## DISCUSSION

Phlebitis migrans is the characteristic finding that Buerger emphasized, for distinguishing Buerger disease[1] from juvenile arteriosclerosis. Furthermore, he reported that a thrombus is seen in high frequency in not only the superficial vein, but also in a deep vein. Shionoya regards the frequency of examinations for Buerger disease as around 40%, and because of the low frequency, either arterial occlusion of the upper extremity or/and phlebit's migrans determines it to be one of the diagnostic criteria. In his criteria, phlebitis is not an essential point for diagnosis.[3]

When the reddish phlebitis portion is removed surgically and is viewed under a microscope, inflamed cells and giant cells are seen. The phlebitis is seen below the knee and mostly around the ankle.[4] On the other hand, pigmentation can be from various causes, though it is not diagnosed as phlebitis in a Buerger disease patient.

It is not clear whether phlebitic veins are patent or occluded after the diagnosis of phlebitis.[5] Possibly related to the decrease of cases in developed countries, the report on the reflux of the vein examined by duplex or the color Doppler methods is not found in the literature. In examinations only by venography performed in the 1970s, abnormalities were reportedly observed in around 60% of the cases.[2] Still further, because the acute phase of phlebitis seemed to involve infection, Buerger doubted infection, but was unable to prove it.[1] Our results suggested that the presence of periodontal bacteria in the veins destroys the vein and lead to the venous valve dysfunction. However, a 41 year-old male patient showed phlebitis migrans on the great saphenous vein. The ultrasound examination revealed that the saphenous vein was occluded. This may mean that the pathogenesis of the venous reflux has two sources; namely direct damage or indirect valve damage by thrombus.

Sakaguchi suggested that the phlebitis lead to expression of the arterial lesion and thought it was connected to etiology discovery.[6]

In 2002, we found and reported that oral bacteria DNA is present in the occluded arterial part of Buerger disease for the first time and also reported elevation of IgG titer to periodontal pathogens.[7,8] Furthermore, when we discovered that oral bacteria enters platelets and forms lumps, we were able to show that oral bacteria are carried from the oral cavity into the circulating blood system safely.[9]

Our hypothesis is that the main cause is an embolism of aggregated mass in a platelet, including oral bacteria; young people, even heavy smokers, have healthy endothelial tissue, which makes it difficult to explain that the main cause is an adhesive or endothelial problem of a young man. Interestingly, the onset process of phlebitis or systemic occlusion of the entire body is easily explained using this hypothesis (**Fig. 6**).[9–14]

It is already well known that smoking causes great harm directly to the periodontal area. It is said there is no effective treatment for the diseased teeth of a smoker.[10,11,13,14] Smokers suffer from weak bacterial infections that keep bacteria around the teeth; the bacteria

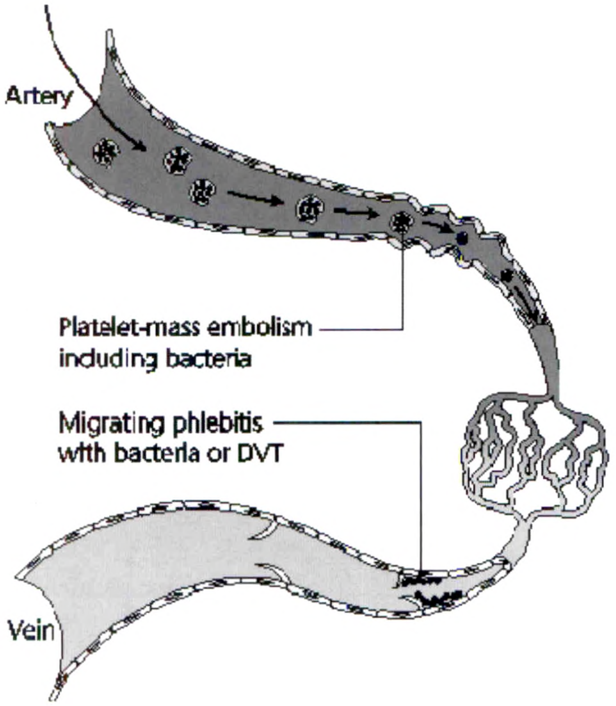
Artery
Platelet-mass embolism including bacteria
Migrating phlebitis with bacteria or DVT
Vein

**Fig. 6** Hypothesis for the development of Buerger disease, deep vein thrombosis, and phlebitis migrans.

enter the platelets and is transported around the body. It was not surprising to find extra-peripheral arterial involvement, such as cerebral, coronary, visceral arteries, and so on with Buerger disease-like occlusions.[5] It seems that fingers and toes easily become symptomatic and small embolisms occur in comparison with the other bigger organs containing phagocytes.

As a result, I can understand how oral bacteria, which passe through a capillary, may cause acute inflammation in a vein of the foot, and that the various kinds of inflammation reactions in the phlebitis migrans have been observed and reported.[15–17] It is thought that oral bacteria will move up the foot vein slowly, destroying the vein valve with an inflammatory reaction.[18] There were few cases this time for a DNA PCR study, but disease from oral bacteria was still found in 75% of the phlebitis migrans. By the way, Kurihara reported that the frequency of oral bacteria expression for the primary varicose veins is 48%.[15]

We would like to further discuss recent cases and also our results, in which we observed the valve function. The primary varicosity is developed when a valve is incompetent, but nobody knows how and when it progresses from which part. It is said that phlebitis migrans of Buerger disease appears in the leg or the ankle region. Our study suggested that saphenous vein incompetence is mainly observed but branch vein incompetence is also present. In addition, three cases showed an ulcer and erosion. One ulcer was deep, and in this case (**Fig.s 1** and **3**) was treated as an ischemic ulcer by his personal physician for a long time. Furthermore, even if there is reflux, the meandering of the vein seems to be characteristically unremarkable. The genetic differences that we examined, as well as the smoking frequency of males, will explain why men are so much more vulnerable than women.[19]

Generally, for ischemic lower limbs, elastic stockings are considered to be contraindicated. However, when the arterial condition becomes chronic, elastic stockings were effective in alleviating symptoms. And from personal experience, the ankle-brachial pressure index should be near or greater than 0.7 and there should be no acute ischemic signs or symptoms in the toes.

Ligation of the incompetent vein, and foam sclerotherapy are effective, too. However, our job is to sufficiently understand how to treat the ischemic limb and to provide an adequate explanation to the patient.

## CONCLUSION

Three out of four venous samples of phlebitis migrans showed oral bacterial DNA by PCR. With 24 Buerger disease patients, moderate varicosity with vein incompetence by duplex was observed in 65%. Of those, three patients demonstrated a chronic ulcer or erosion. The ulcer or erosion was healed completely by the reflux treatment. As for Buerger disease, the subject of the treatment is utilized only for artery ischemia. However, in our hypothesis, the observation of a vein is necessary.

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**Original Article**

# Autologous Peripheral Blood-Derived Mononuclear Cells Induced by Erythropoietin Improve Critical Ischemic Limbs

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Tetsuya Kitagawa, MD, PhD[1]

***Purpose:*** **Efficient and secure collection of CD34+ cells are crucial for the angiogenic therapies. We have developed autologous peripheral blood-mononuclear cell (MNC) transplantation induced by erythropoietin (rhEPO) for critical ischemic limbs.**

***Methods:*** **Seven patients, including five with arteriosclerosis obliterans, one with Buerger's disease and one with progressive systemic sclerosis, underwent ten cell therapies. The first administration of rhEPO was performed two weeks before apheresis, and the second administration and blood donation were performed one week before apheresis to activate bone marrow. MNCs including CD34+ cells, isolated from peripheral blood by apheresis, were immediately injected intramuscularly into ischemic limbs.**

***Results:*** **The number of peripheral blood-CD34 + cells had significantly increased from 1.32 ± 0.83/microL, before the rhEPO induction, to 1.86 ± 0.94/microL, before the apheresis. The number of transplanted MNCs ranged between $0.5 \times 10^9$ and $16.5 \times 10^9$, and that of CD34+ cells, between $0.1 \times 10^6$ and $12.7 \times 10^6$, accounting for 0.02%–0.1% of MNCs. There were no serious complications. Finger ulcers with Buerger's disease were significantly improved one month after the transplantations, but the same or other ulcer(s) appeared 2–6 months later. Three patients had an improvement in rest pain, and one patient extended maximum pain-free walking distance.**

***Conclusions:*** **Erythropoietin-induced autologous peripheral blood-MNC transplantation is a useful and safe alternative for ischemic limbs.**

***Keywords:*** erythropoietin, angiogenesis, autologous peripheral blood-derived mononuclear cell transplantation, critical ischemic limbs

## INTRODUCTION

Despite the accumulation of clinical results of therapeutic angiogenesis using autologous bone marrow- or peripheral blood-derived mononuclear cells, there are still no absolute perspectives related to the efficacy and mechanism.[1–7)] Practical, less-invasive and easily applicable therapeutic angiogenesis remains to be established.

Recombinant human granulocyte colony-stimulating factor (G-CSF) has been used clinically to mobilize peripheral blood progenitor cells for hematopoietic cell transplantation and granulocytes for apheresis collection.[8)] However, angina has frequently occurred after

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G-CSF-induced mobilization of peripheral blood progenitor cells in patients with advanced coronary artery disease.[9] Spontaneous splenic rupture secondary to high-dose G-CSF use (20 mcg/kg/day) was also observed in a healthy allogeneic donor of peripheral blood progenitor cells.[10] On the other hand, human recombinant erythropoietin (rhEPO) has been used safely in a clinical setting for renal anemia, and hematopoietic and endothelial cell lineages seem to share common progenitors.[11,12] Erythropoietin has direct biologic effects on endothelial cells, and the vasculature seems to be an important erythropoietin target. Recently, a significant mobilization of CD34+/CD45+ circulating progenitor cells in peripheral blood was observed by rhEPO administration.[13]

We have newly developed autologous peripheral blood-derived mononuclear cell (MNC) transplantation induced by erythropoietin and blood donation for activating the function of bone marrow, and have been performing this cell transplantation therapy for patients with critical ischemic limbs since 2004. The aim of the present study was to determine the efficacy and safety of the cell transplantation therapy as a therapeutic option for critical ischemic limbs.

## MATERIALS AND METHODS

### Indication of autologous peripheral blood-derived mononuclear cell transplantation

Cell therapy was indicated for selected patients whose activities of daily living were extremely disturbed and who did not show any favorable response to medication or conservative and surgical treatments for critical ischemic limbs. Exclusion criteria of the cell therapy were as follows: 1) life expectancy of less than one year, 2) history of alcohol or drug abuse within the past 3 months, 3) malignant tumor or possibility of malignant tumor, 4) history of the malignant tumor within the past 5 years, 5) diabetic proliferative retinopathy, 6) untreated severe ischemic heart disease, and 7) pregnancy or possibility of pregnancy. The institutional review board of Tokushima University Hospital (Clinical Research Number 158) approved the protocol of this study, and written informed consent was obtained from all subjects.

### Protocol of peripheral blood-derived mononuclear cell transplantation

RhEPO and blood donation-induced mobilization of peripheral blood-progenitor cells was performed as follows: 1) 6000 IU of rhEPO of was administered subcutaneously two weeks before apheresis, 2) additional subcutaneous administration of 6000 IU of rhEPO and 400 ml of donated blood was performed one week before apheresis, 3) peripheral blood-derived MNCs were collected by apheresis using COBE Spectra$^{TM}$ two weeks after the first rhEPO injection, and 4) the cells were implanted intramuscularly into ischemic limbs (50-100 points) just after the apheresis under epidural or general anesthesia for upper extremities.

### Assessment of critical limb ischemia

*1) Augmentation of CD34+ mononuclear cells in peripheral blood*

Levels of circulating CD34+, CD34+/CD133+ and CD34+/CD14+ cells in peripheral blood of the enrolled patients were measured by flow cytometry before and after apheresis. CD34 is a marker for hematopoietic progenitor cells, CD133, a marker for hematopoietic or non-hematopoietic progenitor cells, and CD14, a marker for monocytes. Increase in the number of CD34+ cells, in peripheral blood, by the above-mentioned induction was followed before the first and second rhEPO administrations and before apheresis. CD45+ is a marker for leukocyte common antigen. The numbers of peripheral-blood CD34+ cells were calculated by the formula (CD34+/CD45+ cells x the count of white blood cell/microL). The numbers of MNCs and CD34+ cells of the product harvested by apheresis were calculated separately from them.

*2) Assessment of cell therapy for limb ischemia*

The efficacy and safety of cell transplantation therapy for critical ischemic limbs were assessed before and at 1, 2, 3 and 4 weeks and 3 and 6-months after cell transplantation by 1) the rest-pain scale of ischemic limbs, 2) clinical findings of ischemic limbs (ulcer and gangrene), 3) ankle-brachial pressure index, 4) photoplethysmography, 5) thermography, 6) laser doppler perfusion imaging, 7) transcutaneous oxygen and carbon dioxide tensions ($TcPO_2$ and $TcPCO_2$), and 8) digital subtraction angiography.

### Patients' characteristics

Seven patients with critical ischemic limbs (male/female = 6/1), including 5 patients with arteriosclerosis obliterans (ASO), one patient with Buerger's disease and

**Table 1 Patients' characteristics at first cell therapy**

| Case No. | age (ys.) | Diagnosis | Status of Limb ischemia | Previous treatment | Characteristics |
|---|---|---|---|---|---|
| 1. | 77 | ASO | rest pain | Femoro-popliteal bypass, medication | lumbar spinal canal stenosis |
| 2. | 68 | ASO | rest pain | Femoro-popliteal bypass, medication | DM, HL, S/P CABG, CRF on HD |
| 3. | 66 | ASO | rest pain | medication | DM, HL |
| 4. | 45 | ASO | toe gangrene rest pain | Aorto-femoral bypass, medication | smoking |
| 5. | 61 | ASO | toe gangrene rest pain | medication | S/P CABG, CRF on HD, cerebral hemorrhage |
| 6. | 48 | Buerger | finger ulcers rest pain | medication | DM, HL |
| 7. | 79 | PSS | toe gangrene rest pain | medication | DM, HL, cerebral infarction |

ASO: arteriosclerosis obliterans; PSS: progressive systemic sclerosis; DM: diabetes mellitus; HL: hyperlipidemia; S/P CABG: postoperative state of coronary artery bypass grafting; CRF on HD: chronic renal failure on hemodialysis

one patient with progressive systemic sclerosis (PSS), were enrolled in this study during the period from 2004 to 2010 (**Table 1**). Only the patient with Buerger's disease and intractable finger ulcers underwent cell therapy four times, and overall cell therapy was performed ten times. The ages of patients who underwent cell therapy ranged from 45 to 79 years (61 ± 13 years). The patient with Buerger's disease complained of intractable pain and finger ulcers. The patient with progressive systemic sclerosis and two patients with ASO exhibited toe gangrene, and the remaining three patients with ASO had rest pain. Two of the patients with ASO suffered from chronic renal failure and were on hemodialysis.

### Statistical analysis

Changes in the number of peripheral blood-CD34+ cells were expressed as percentages of the number before the 1st rhEPO administration (mean ± SD). Statistical comparisons were performed using the paired Student's t-test, with a probability value of less than 0.05 taken to indicate significance.

## RESULTS

Laboratory examinations showed no polycythemia due to rhEPO administration or anemia due to phlebotomy but showed an increase in reticulocytes indicating activation of bone marrow (**Table 2**).

### 1) Augmentation and collection of CD34+ mononuclear cells in peripheral blood by erythropoietin administration and blood donation

Fluorescence–activated cell storing analysis of peripheral blood using CD34, CD133 and CD14 cells before and after apheresis demonstrated effective collection of peripheral blood-derived MNCs including CD34+ cells (**Fig. 1A**). The change of the number of peripheral blood-CD34+ cells in each patient, not on hemodialysis, is shown from before the 1st rhEPO administration to before apheresis in **Fig. 1B**. The number of peripheral blood-CD34+ cells had increased from 1.32 ± 0.83/microL before the rhEPO induction to 1.92 ± 1.29/microL before the 2nd rhEPO administration and to 1.86 ± 0.94/microL before apheresis (**Fig. 1B**). There was a significant difference between the number of peripheral blood CD34+ cells before the 1st rhEPO administration and that before apheresis. The number of MNCs harvested by apheresis ranged between $0.5 \times 10^9$ and $16.5 \times 10^9$ (mean ± SD, $10.0 \times 10^9 \pm 4.7 \times 10^9$). Consequently, the number of CD34+ cells in the product harvested by apheresis ranged between $0.1 \times 10^6$ and $12.7 \times 10^6$ ($6.5 \times 10^6 \pm 4.5 \times 10^6$) and accounted for 0.06 ± 0.03% (0.02%–0.1%) of the MNCs (**Table 3**). Induction of peripheral blood CD34+ cells was performed without any serious complications; however, patients over 65 years of age or with chronic renal failure patients on hemodialysis had small numbers of peripheral blood CD34+ cells in the harvested MNCs.

**Table 2 Laboratory examination around rhEPO and blood donation-induced mobilization of peripheral blood-derived progenitor cells and apheresis in a patient with Buerger's disease**

| | 1st Cell Therapy | | | | 2nd Cell Therapy | | | | 3rd Cell Therapy | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Base line | 2nd EPO | pre Aphe | post Aphe | Base | 2nd EPO | pre Aphe | post Aphe | Base | 2nd EPO | pre Aphe | post Aphe |
| | 5/10/'05 | 5/18 | 5/23 | 5/24 | 8/11/'05 | 8/19 | 8/24 | 8/25 | 4/30/'08 | 5/09 | 5/14 | 5/15 |
| WBC (*$10^3$/uL) | 6.8 | 8.1 | 8.8 | 7.1 | 6.6 | 10.3 | 8.3 | 8.2 | 7.7 | 8.4 | 9.1 | 7.9 |
| RBC (*$10^6$/uL) | 4.26 | 4.31 | 4.31 | 4.02 | 4.52 | 4.46 | 4.07 | 3.99 | 4.10 | 4.04 | 3.78 | 3.57 |
| Hemoglobin (g/dL) | 14.2 | 14.2 | 14.3 | 13.4 | 15.2 | 15.2 | 13.7 | 13.8 | 14.3 | 14.2 | 13.0 | 12.3 |
| Platelet (*$10^3$/uL) | 343 | 309 | 319 | 251 | 276 | 306 | 333 | 287 | 305 | 363 | 407 | 323 |
| Reticulocyte (‰) | 17 | 25 | 30 | 28 | 21 | 30 | 27 | 23 | 17 | 29 | 27 | 26 |
| Neutrophil (%) | 60.2 | 62.5 | 60.9 | 67.8 | 72.6 | | 58.9 | 80.1 | 68.5 | 64.4 | | 72.8 |
| Lymphocyte (%) | 29.1 | 27.3 | 27.7 | 21.9 | 18.8 | | 30.9 | 11.3 | 22.6 | 24.4 | | 17.0 |
| Monocyte (%) | 6.1 | 5.9 | 6.1 | 6.5 | 5.0 | | 6.4 | 6.5 | 5.3 | 6.4 | | 6.9 |

No polycythemia due to rhEPO administrations or anemia due to blood donation were shown. Reticulocytes were increased from 17–21‰ to 25–30‰ by human recombinant erythropoietin administrations and blood donation indicating activation of bone marrow. EPO: human recombinant erythropoietin; Aphe: apheresis; Base line: before the 1st rhEPO administration; 2nd EPO: after the 2nd rhEPO administration; preAphe: before apheresis; postAphe: after apheresis

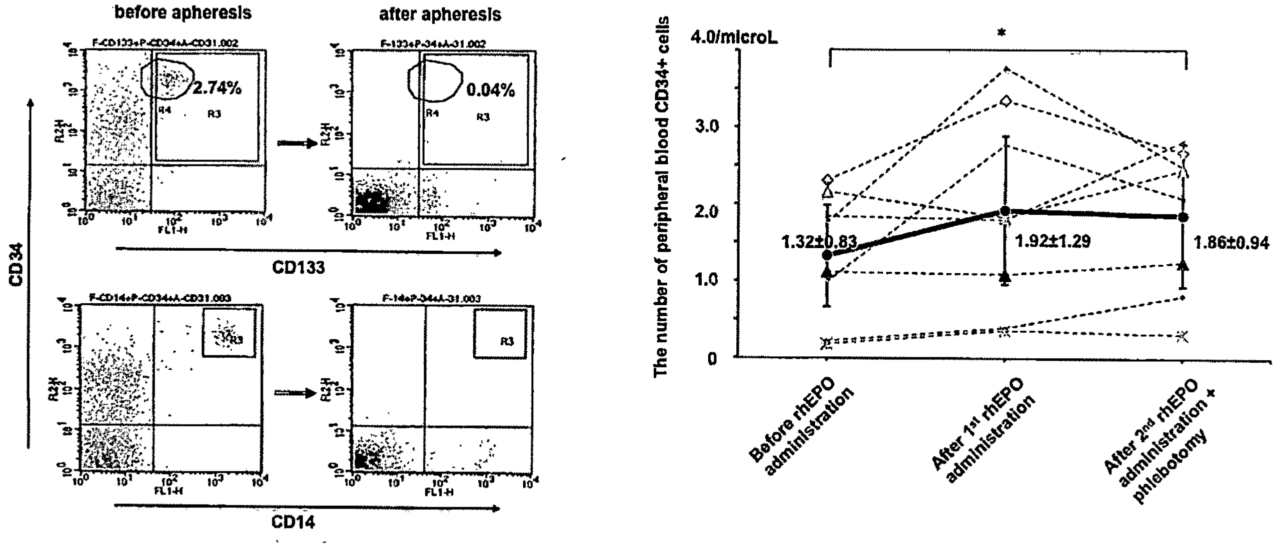

**Fig. 1**

A | B

**A**: Fluorescence–activated cell storing analysis of peripheral blood using CD34, CD133 and CD14 cells before and after apheresis. The results of peripheral blood-cell sorting analysis of patient 1 are shown. CD34+/ CD133+ mononuclear cells were effectively collected from peripheral blood by apheresis.

**B**: Changes in the number of CD34+ cells in peripheral blood of patients not on hemodialysis from before the 1st rhEPO administration to before apheresis. Peripheral blood CD34+ cells increased to 159 ± 64% (82%–245%) before the 2nd rhEPO administration and to 137 ± 35% (88%–175%) before apheresis. There was a significant difference between the percentage of peripheral blood CD34+ cells before the 1st rhEPO administration and that before apheresis.

rhEPO: human recombinant erythropoietin

**Table 3 The number of implanted mononuclear cells, CD34+ cells, and % of CD34+ cells**

| Case No. | age (yrs.) | Diagnosis | MNCs (no.) | CD34+ cells (no.) | % of CD34+ cells |
|---|---|---|---|---|---|
| 1. | 77 | ASO | $0.5 \times 10^9$ | $0.1 \times 10^6$ | 0.02 |
| 2. | 68 | ASO (on HD) | $9.0 \times 10^9$ | $2.7 \times 10^6$ | 0.03 |
| 3. | 66 | ASO | $16.5 \times 10^9$ | $5.0 \times 10^6$ | 0.03 |
| 4. | 45 | ASO | $12.7 \times 10^9$ | $12.7 \times 10^6$ | 0.10 |
| 5. | 61 | ASO (on HD) | $10.0 \times 10^9$ | $4 \times 10^6$ | 0.04 |
| 6. -1st. | 48 | Buerger | $9.2 \times 10^9$ | $9.2 \times 10^6$ | 0.10 |
| -2nd. | 48 | Same as above | $16.1 \times 10^9$ | $12.7 \times 10^6$ | 0.08 |
| -3rd. | 51 | Same as above | $10.3 \times 10^9$ | $9.7 \times 10^6$ | 0.09 |
| -4th. | 53 | Same as above | $10.6 \times 10^9$ | $7.4 \times 10^6$ | 0.07 |
| 7. | 79 | PSS | $5.3 \times 10^9$ | $1.58 \times 10^6$ | 0.03 |
| Mean ± SD | 61 ± 13 |  | $10.0 \times 10^9 \pm 4.7 \times 10^9$ | $6.5 \times 10^6 \pm 4.5 \times 10^6$ | 0.06 ± 0.03 |

ASO: arteriosclerosis obliterans; PSS: progressive systemic sclerosis; MNC: mononuclear cell; % of CD34+ cells: the number of CD34+ cell/the number of mononuclear cell

**Table 4 Outcomes of limb ischemia after cell therapies**

| Case No. | Diagnosis | Status of limb ischemia before cell therapy | Outcome of limb ischemia rest-pain scale (before→after) | Maximum walking distance after cell therapy (before→after) | Adverse complications |
|---|---|---|---|---|---|
| 1. | ASO | rest pain | rest-pain scale (7→7) | wheelchair | none |
| 2. | ASO | rest pain | rest-pain scale (10→5) | 48m→100m | none |
| 3. | ASO | rest pain | rest-pain scale (2→0) | 160m→915m | none |
| 4. | ASO | toe gangrene<br>rest pain | amputation | / | none |
| 5. | ASO | toe gangrene<br>rest pain | amputation | / | none |
| 6. -1st. | Buerger | finger ulcer<br>rest pain | temporarily improved<br>rest-pain scale (6→3) | / | none |
| -2nd. |  | finger ulcer<br>rest pain | temporarily improved<br>rest-pain scale (3→1) | / | none |
| -3rd. |  | finger ulcer<br>rest pain | temporarily improved | / | none |
| -4th. |  | finger ulcer<br>rest pain | temporarily improved | / | none |
| 7. | PSS | toe gangrene<br>rest pain | amputation | / | none |

ASO: arteriosclerosis obliterans; PSS: progressive systemic sclerosis; rest-pain scale of ischemic limbs (before cell implantation→6 months after cell implantation)

### 2) Outcomes of critical limb ischemia after cell transplantation

There were no adverse complications caused by the trials (**Table 4**). Three patients showed subjective improvement in the rest-pain scale of ischemic limbs and exhibited objective appearance of pulse waves in a toe photoplethysmogram. Only one patient showed notable improvement of maximum pain-free walking distance from 160m before cell transplantation to 915m after cell transplantation. The two patients with ASO and the patient with PSS associated with advanced toe/foot gangrene required amputation of the lower limb within 3 months after cell transplantation.

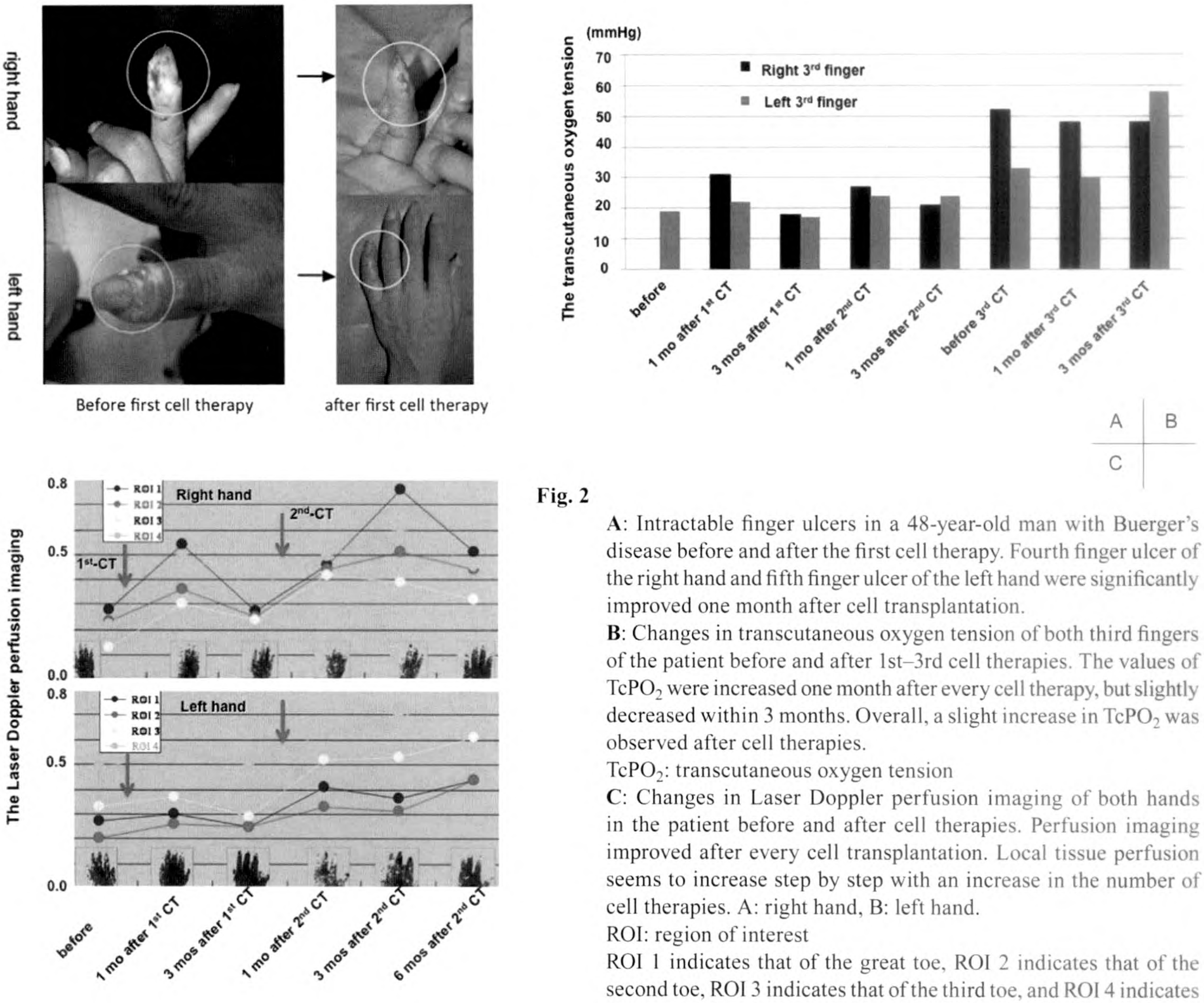

**Fig. 2**

**A**: Intractable finger ulcers in a 48-year-old man with Buerger's disease before and after the first cell therapy. Fourth finger ulcer of the right hand and fifth finger ulcer of the left hand were significantly improved one month after cell transplantation.

**B**: Changes in transcutaneous oxygen tension of both third fingers of the patient before and after 1st–3rd cell therapies. The values of $TcPO_2$ were increased one month after every cell therapy, but slightly decreased within 3 months. Overall, a slight increase in $TcPO_2$ was observed after cell therapies.

$TcPO_2$: transcutaneous oxygen tension

C: Changes in Laser Doppler perfusion imaging of both hands in the patient before and after cell therapies. Perfusion imaging improved after every cell transplantation. Local tissue perfusion seems to increase step by step with an increase in the number of cell therapies. A: right hand, B: left hand.

ROI: region of interest

ROI 1 indicates that of the great toe, ROI 2 indicates that of the second toe, ROI 3 indicates that of the third toe, and ROI 4 indicates that of the fourth toe. Y-axis shows the value (voltage) of mean perfusion in each ROI.

A 48-year-old man with Buerger's disease and intractable finger ulcers underwent successful 1st cell transplantation. Clinical symptoms with finger ulcers had significantly improved one month after MNC transplantation; however, an intractable ulcer on the same finger appeared two months later (**Fig. 2A**). Intermittent MNC transplantations were performed four times. Each cell transplantation resulted in an improvement, one month later, and the appearance of an ulcer(s) on the same/other finger ulcer(s) 2–6 months later. Laser Doppler perfusion imaging (LDPI) and $TcPO_2$ data showed an increase in peripheral tissue blood flow step by step with increase in the number of cell therapies (**Fig. 2B** and **2C**).

## DISCUSSION

Some angiogenesis therapies, using endothelial progenitor cells or extended modifications for peripheral arterial disease, were exploited, according to its basic rule, since the Japan Trial for Therapeutic Angiogenesis Using Cell Transplantation and have been in clinical use.[5] In particular view of safety concerns, clinical use of the several therapeutic angiogenesis using autologous bone marrow- or peripheral blood-derived MNCs have been accumulated, however, the superior efficacy of those cell therapies has not yet been achieved.[9,10,14–16] Practical, less-invasive and easily applicable therapeutic angiogenesis remains to be established. Peripheral blood MNC transplantation is expected to be developed as an efficient and safe optional treatment for critical ischemic limbs.

## Mechanistic explanation of how transplanted mononuclear cells work in critical ischemic limbs

The patient who had symptoms that were most suggestive of Buerger's disease and intractable finger ulcers underwent four successful cell transplantations that resulted in an improvement, one month later, though the patients had a relapse of the same/other finger ulcer(s), 2–6 months later. Clinical improvement of the finger ulcers coincided with the timing of peak values of local LDPI and $TcPO_2$, after each cell therapy. Those facts imply that the cell therapy itself plays some role in healing ischemic ulcers and that its working mechanism was through the upregulation of some tissue cytokines such as classic angiogenic growth factors consequent to the transplanted MNCs.[17–21] There was a recent report that human CD34+ exosomes may represent a significant component of the paracrine effect of progenitor cell transplantation for therapeutic angiogenesis.[22] Not only the long survival and the increase of transplanted MNCs, but also the potential of paracrine effects provided by the local secretion of cytokines, may underlie the longevity of improvement of ischemic limbs. In particular, the anti-apoptosis effect of augmented cytokines may result in the improvement. The resident population of apoptotic cells that are competent to respond to cytokines may also constitute a potentially limiting factor in those cell therapies. Since there was a long period (up to 6 months) until disappearance of finger ulcers, a more progressed cell therapy, with fine conservative management, will provide complete remission of finger ulcers in the near future. It is necessary to further investigate how rhEPO-induced MNCs participate in the restoration of damaged tissue circulation.

## Role of erythropoietin induction in the cell therapy

Erythropoietin can induce endothelial cell proliferation and differentiation and accelerate the migration of endothelial progenitor cells to peripheral blood.[11] Erythropoietin levels were significantly increased on the day of peripheral blood stem cell collection, 2 weeks after chemotherapy, and G-CSF administration in comparison with levels of other cytokines.[23] Exposure to moderate hypoxia leads to an increase in progenitor cells in tissue and circulation, the effect of which is dependent on erythropoietin.[24] Serum levels of erythropoietin are significantly associated with the number and function of circulating endothelial progenitor cells as well as with the number of progenitor cells in bone marrow and may help in identifying patients with impaired endothelial progenitor cell recruitment capacity. Strategies that increase serum erythropoietin concentrations may be promising for augmenting the regenerative properties of peripheral blood progenitor cells.

Although therapeutic angiogenesis, using many CD34+ cells from bone marrow, has been introduced in patients with peripheral artery disease, the invasiveness limits clinical application for cell therapy.[1] On the other hand, therapeutic angiogenesis using peripheral blood-derived MNCs is less invasive, and it also has the disadvantage of a small number of MNCs harvested by apheresis. Endothelial progenitor cells consist of about 0.01% of bone marrow-derived MNCs, and those of peripheral blood-derived MNCs is also anticipated being extremely low.

## Pathophysiological factors influencing the efficacy and safety of the cell therapy

Other investigators have demonstrated that the number of peripheral blood-derived MNCs induced by G-CSF for cell therapy to ischemic limbs was 2.3-11.6 × $10^{10}$ and that the number of CD34+ cells was 1.37-14.9 × $10^7$ (mean, 0.13%; 0.07%–0.29%).[25,26] Pretreatment with rhEPO caused significant mobilization of CD34+ circulating progenitor cells in peripheral blood and increased the number of functionally active endothelial progenitor cells in patients (week 2, 312 ± 31%; week 8, 308 ± 40%) as well as in healthy subjects (week 8, 194 ± 15%).[11] Our previous study also revealed that the combination of rhEPO administration and blood donation resulted in a significantly greater increase in the number of CD34+ and CD34+/CD133+ MNCs than that in the case of blood donation only and that rhEPO administration was a significant independent factor for the magnitude of increase in CD34+/CD133+ MNCs.[27] The results of the present study suggest that the optimal timing of apheresis for cell therapy is one week after 2nd rhEPO administration and blood donation as our protocol.

Although the mechanisms by which stem cells might contribute to angiogenesis and the origin of neovascular endothelial cells are controversial,[22,28] our results seem to imply that the efficacy of induction of autologous peripheral blood-derived MNCs by rhEPO and blood donation is dependent on the number of transplanted CD34+ cells and the patient's pathogenesis. Among patients less than 55 years of age or without chronic renal failure requiring hemodialysis, CD34+ cells were increased to 0.07%–0.1% of MNCs by our scheduled induction, and 9.2-16.1 × $10^9$ MNCs and 7.4-12.7 × $10^6$ CD34+ cells were transplanted to ischemic limbs. Although the augmentation by rhEPO was inferior to that by G-CSF, peripheral blood MNCs induced by rhEPO showed subjective and objective improvements to some degree without serious adverse effects such as angina and myocardial infarction. The acuity of ischemic limbs seems to be a limiting factor, and recipients with Buerger's disease may be more favorable than those with ASO.29) In any case, early cell transplantation therapy is recommended as an optional treatment for selected patients with peripheral arterial disease.

## CONCLUSIONS

The findings suggest that autologous peripheral blood-mononuclear cell transplantation induced by rhEPO is a useful and safe alternative for patients with peripheral arterial disease, particularly for patients with Buerger's disease and intractable finger ulcers.

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**Case Report**

# Hybrid Repair Combined with Open Surgery and Endografting for Lesions in Right Aortic Arch: Report of Three Cases

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**Three cases with lesions in the right aortic arch (RAA) are presented. For two patients, whose RAA contained a retroesophageal segment, the primary treatment was total arch replacement (TAR) for acute type A dissection or severe arch angulation with thoracic endovascular aneurysm repair (TEVAR) as second-stage surgery. The third patient, who had RAA with mirror image branching, underwent supra-aortic bypass followed by TEVAR. There was no operative mortality, but the condition of two patients who underwent TAR was complicated by bilateral recurrent nerve palsy, which can be critical. The combination of TEVAR and supra-aortic bypass might thus be preferable for patients with RAA.**

***Keywords:*** right aortic arch, stentgraft, TEVAR, endovascular repair, hybrid repair

## INTRODUCTION

Right aortic arch (RAA) is a relatively common anomaly which is classified by double or single arch and is categorized by a retroesophageal segment.[1)] The surgical treatment for aortic lesions involving RAA is complicated due to the anatomical relationship of the aorta with the trachea and esophagus, and exposure of all aortic segments may be possible only through a median sternotomy or an intercostal thoracotomy. However, thoracic endovascular aneurysm repair (TEVAR) is a viable therapeutic alternative for treatment of the descending aorta running on both sides of pleural cavities. The advantage of hybrid aortic repair utilizing TEVAR for patients with RAA is discussed.

## PATIENTS

Clinical charts of three cases with RAA who underwent hybrid aortic repair were reviewed retrospectively.

Case 1 was a 67-year-old man who had been diagnosed with an infrarenal abdominal aortic aneurysm (AAA). He presented with sudden, severe back pain, and enhanced computed tomography showed an acute type A aortic dissection, associated with RAA. The right subclavian (RSCA), right common carotid (RCCA), left common carotid (LCCA), and left subclavian (LSCA) arteries branched in that order from the RAA with a retroesophageal segment. For emergency surgical treatment of the aortic dissection, the heart and the aorta were exposed through a median sternotomy. A cardiopulmonary bypass with bicaval venous drainage was then initiated via the right axillary and left common femoral arteries. When the RAA was opened under deep hypothermia and selective cerebral perfusion, it was found that Kommerell's diverticulum behind the esophagus could not be approached because its location was too deep. Total arch replacement was, therefore, indicated, and distal anastomosis was initiated proximally to the diverticulum. To cover the entry, we inserted a 7-cm long elephant trunk graft into the true lumen of the descending aorta.

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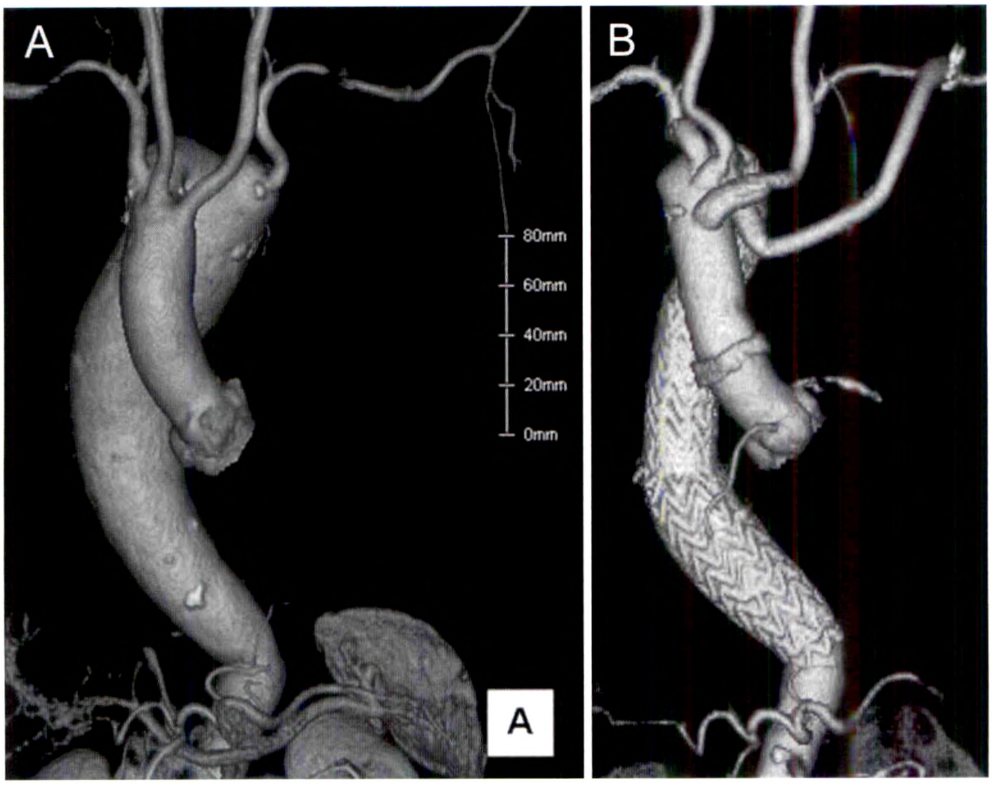

**Fig. 1**

(**A**) Case 2 developed dilatation of Kommerell's diverticulum and consequent descending aortic aneurysm (52 mm) with RAA containing a retroesophageal segment. The orifices of the LCCA, RCCA, and RSCA were close together at the top of the RAA and the LSCA arose from the diverticulum.

(**B**) Case 2 underwent total arch replacement and elephant trunk installation to create an adequate landing zone, and TEVAR with GoreTAGs (28 mm × 15 cm and 34 mm × 20 cm) was performed one week later, extending from the elephant trunk to the distal descending aorta.

LCAA: left common carotid ; RCCA: right common carotid ; RSCA: right subclavian ; RAA: right aortic arch ; LSCA: left subclavian: TEVAR: thoracic endovascular aneurysm repair

The patient's postoperative course was uneventful except for hoarseness due to bilateral recurrent nerve palsy. AAA replacement was performed 3 months later. For enlargement (58 mm) of the middle descending aorta, TEVAR with GoreTAG (26 mm × 10 cm) was performed, extending from the elephant trunk to the distal descending aorta. One year postoperatively, the descending aorta showed no further enlargement.[2)]

Case 2 was a 74-year-old male who developed dilatation of Kommerell's diverticulum and consequent descending aortic aneurysm (52 mm). The RAA contained a retroesophageal segment (**Fig. 1**), and the orifices of the LCCA, RCCA and RSCA were close together at the top of the RAA, while the LSCA arose from the diverticulum. Total arch replacement and elephant trunk installation were performed to create an adequate landing zone while TEVAR with GoreTAGs (28 mm × 15 cm and 34 mm × 20 cm) was performed, extending from the elephant trunk to the distal descending aorta one week later. The patient developed postoperative, bilateral recurrent nerve palsy and pneumonia.

Case 3 was an 81-year-old male with a history of malignant lymphoma. His RAA showed mirror image branching and the left brachiocephalic artery bifurcated to the LSCA, LCCA, RCCA, and RSCA in that order (**Fig. 2**). There were two saccular aneurysms, one just distal to the RSCA and the other at the proximal descending aorta. A supra-aortic bypass from the left axillar artery to the RCCA and right axillar artery was performed and TEVAR with GoreTAG (34 mm × 15 cm) two weeks later. To cope with the acute angle (311-degree) of the RAA, the proximal end of the wrapping of TAG was retracted with a snaring catheter

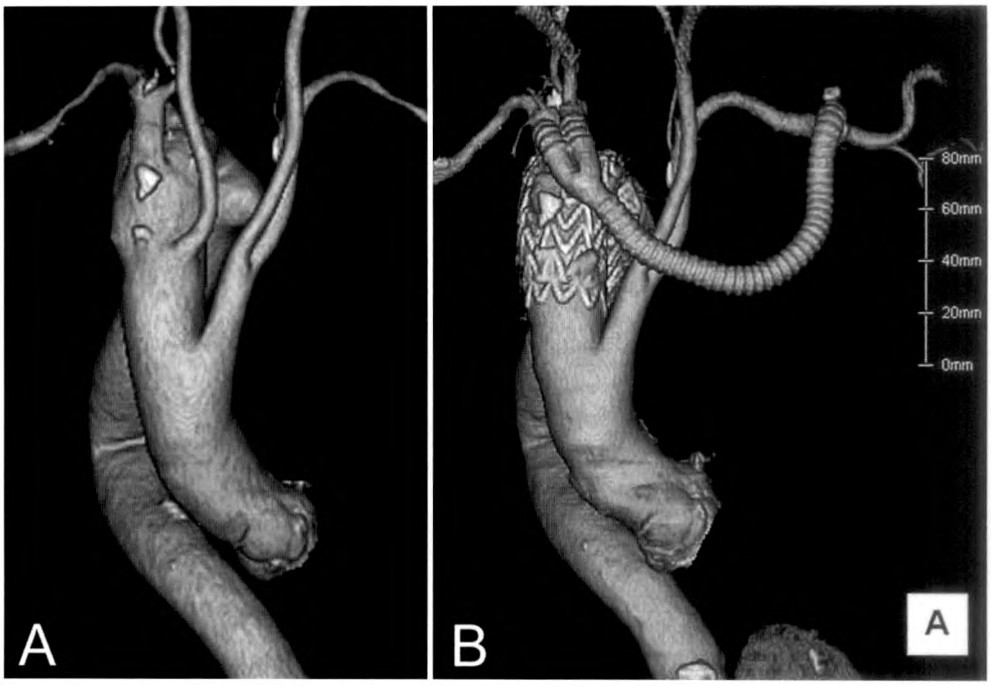

**Fig. 2**

(**A**) Case 3 had RAA with mirror image branching, while the left brachiocephalic artery bifurcated to the LSCA, LCCA, RCCA, and RSCA in that order. There were two saccular aneurysms, one just distal to the RSCA (38 mm) and the other at the proximal descending aorta (50 mm).
(**B**) The case underwent thoracic endografting with GoreTAG (34 mm 15 cm) using the lasso technique two weeks after the bypass operation from the left axillar artery to the RCCA and right axillar artery. To cope with the acute angle (311 degrees) of the RAA, the proximal end of the wrapping of TAG was retracted with a snaring catheter which was inserted from the femoral artery.
RAA: right aortic arch; LSCA: left subclavian; LCAA: left common carotid; RCCA: right common carotid; RSCA: right subclavian

which was inserted from the femoral artery. The patient has been unable to visit our facility because of a pelvic fracture, but his survival was confirmed by telephone interview, one year postoperatively.

## DISCUSSION

The incidence of RAA among adults is reportedly 0.04% to 0.1%.[3,4] The most frequent RAA has no retroesophageal segment or mirror image branching (77%). RAA with a retroesophageal segment is rare (4%).[2] Our basic strategy for treatment of an aneurysm or dissection of the arch is total arch replacement.[3] However, to deal with the risks or problems associated with patients with RAA, we chose hybrid repair including the use of TEVAR for the three cases.

In case 1, the entry tear through the median sternotomy was too deep, and additional treatment was necessary to close the entry. In case 2, the proximal anastomosis for replacement of the descending aorta was deemed too deep to be approached through the thoracotomy over Kommerell's diverticulum. In addition, the orifices of the arch branches were too close together to create an adequate proximal landing zone for TEVAR. Case 3 was too old to undergo total arch replacement. However, RAA with mirror image branches features relatively long distances between the arch branches which allow for preservation of the blood flow to the left brachiocephalic artery and construction of an extrathoracic bypass to the right supra-aortic branches.

Two of the three patients who underwent total arch replacement suffered from bilateral recurrent nerve palsy, and both of them had a retroesophageal aortic segment. In patients with RAA with a retroesophageal aortic segment, the left recurrent nerve approaches the back of the ductus arteriosus, encircles it from the left dorsal lateral to the right ventromedial area, and goes upward along the left surface of the esophagus and trachea, whereas, the right recurrent laryngeal nerve loops the aortic arch from the right dorsal lateral area in the direction of the left ventromedial direction.[4] During the surgery for both these cases, we took great care to preserve the functions of the recurrent nerves, we could not succeed. When total arch replacement is necessary for patients with RAA, such as acute type A aortic dissection, even greater care is needed. When an alternative operative procedure is feasible, the combination of a supra-aortic (extra-thoracic) bypass and TEVAR might be more effective for avoiding this serious complication of bilateral recurrent nerve palsy.

For the combination of total arch replacement and TEVAR, we utilized a synthetic graft to create an elephant trunk as the proximal landing zone for TEVAR. The placement of a stentgraft inside a synthetic graft is not recommended in the instructions for use. However, the utility of this procedure, especially the utilization of an elephant trunk in the extended aneurysm, has been reported.[5]

The RAA tends to have a shorter radius and more acute curvature of the arch than the usual gentle curve of a left aortic arch.[6] In case 2, we anticipated a difficult passage of the GoreTAG through the acute angle, and we, therefore, decided on total arch replacement which turned out to be complicated with bilateral recurrent nerve palsy. In case 3, however, retraction of the GoreTAG with a snaring catheter was found to be useful. Moreover, the gap between the olive tip and the wrapping of stentgraft has been made smoother (TAG over Molded Olive), so that the acute curvature of RAA may no longer be problematic when TEVAR with GoreTAG is used.

A major limitation of this study is the small number of cases with this rare condition. For validation of the long-term durability and efficacy of our strategy, careful follow-up will be essential.[7]

## CONCLUSION

Multiple-stage surgeries including endografting were found to be useful for overcoming anatomical difficulties in patients with RAA. Bilateral recurrent nerve palsy after total arch replacement can be critical, and the use of TEVAR after supra-aortic bypass may, therefore, be preferable for patients with RAA.

## DISCLOSURE STATEMENT

The authors have no conflict of interest to declare.

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**Case Report**

# A Foot Ulcer Caused by the Use of an Angio-Seal Arterial Closure Device after Percutaneous Transluminal Angioplasty: A Case Report

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and Minoru Morimatsu, MD[2]

**Although the Angio-Seal arterial closure device is widely used for preventing bleeding and facilitating early ambulation after arterial puncture, it is also associated with unique complications, such as stenosis, occlusion, or peripheral embolism. We report the first case of a foot ulcer that developed 70 days after an Angio-Seal application. The collagen sponge component accidently positioned itself in the arterial lumen and was not absorbed. A foreign body reaction was observed microscopically. In patients with arteriosclerosis, the Angio-Seal device should be used carefully; post procedural monitoring is necessary after implantation.**

*Keywords:* angio-seal, complication, foot ulcer

## INTRODUCTION

The need for a safe, easy-to-use, and effective hemostatic device has arisen because more percutaneous endovascular procedures are being performed. The Angio-Seal arterial closure device (St Jude Medical, St Paul, MN) is widely used for sealing arterial puncture sites. This device comprises a collagen sponge, an absorbable anchor, and a connecting suture. Such arterial puncture-closing devices are thought to reduce hemostasis time and facilitate early ambulation, which potentially reduces the length of hospital stay and improves patient satisfaction.[1,2] However, these devices have not been shown to reduce access site complications.[1–4] Furthermore, significant complications, such as stenosis, occlusion, or peripheral embolism, may arise from the use of an Angio-Seal device; it is necessary for clinicians to be aware of these complications.[3–8]

We report the case of a patient who presented with a foot ulcer that developed because of the use of an Angio-Seal device.

## CASE REPORT

A 74 year-old woman presented with a right foot ulcer 70 days after percutaneous transluminal angioplasty (PTA), which had been performed at another hospital. She had been undergoing treatment for arteriosclerosis obliterans at our hospital since 4 years earlier. During this treatment period, she showed no symptoms, although her ankle brachial index (ABI) scores were 0.68 and 0.76 for the right and left ankles, respectively. When she was admitted to the hospital for chest pain, PTA performed on the right iliac artery revealed a stenotic lesion, although no significant coronary artery stenosis was observed.

The ABI score deteriorated to 0.55 for the right ankle. Angiography also revealed a severe eccentric stenotic lesion of the right common femoral artery (CFA) at the level of the previous puncture site (**Fig. 1**). The superficial

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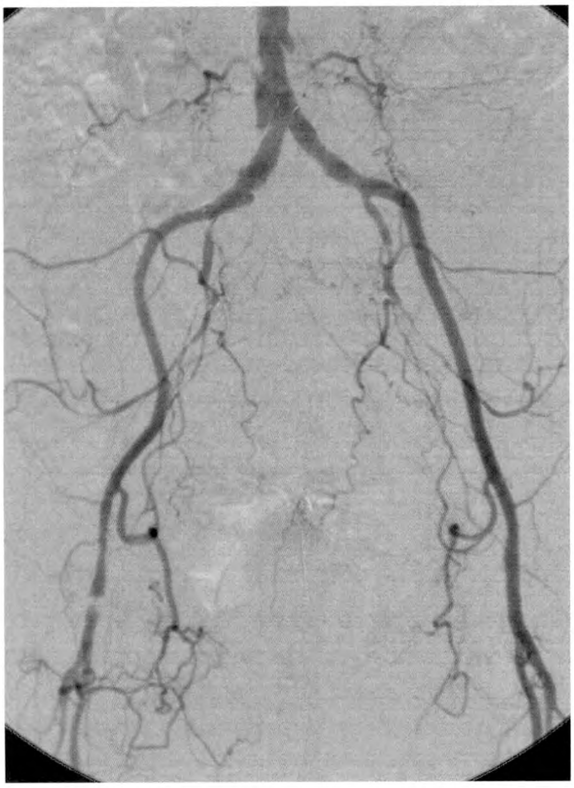

**Fig. 1** Angiography revealed a severe eccentric stenotic lesion in the right common femoral artery (CFA) at the level of the previous puncture site.

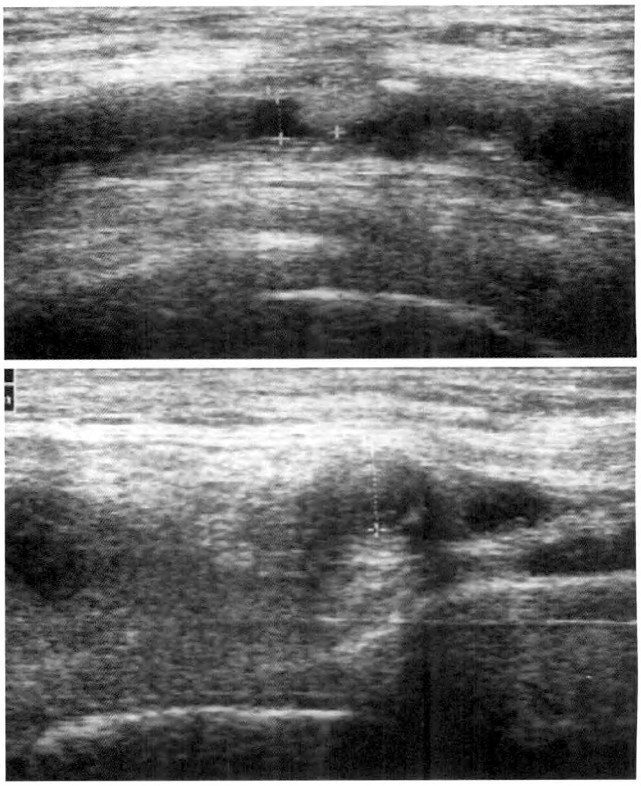

**Fig. 2** Duplex ultrasound scanning showed a severe stenotic lesion due to isoechoic mass.

femoral artery was smooth, although some stenotic lesions were observed in the calf. Duplex ultrasound scanning (DUS) clearly showed a severe stenotic lesion due to an isoechoic mass (**Fig. 2**). This was believed to be a nonatherosclerotic stenosis. We subsequently learned that an Angio-Seal device had been used in the original PTA.

The patient was operated under local anesthesia for treating the rest pain and foot ulcer. A pronounced fibrotic reaction surrounding the groin vessels and advanced arteriosclerosis were detected. Upon opening the CFA, we observed a collagen sponge with a thrombus attached (**Fig. 3**). Since arteriosclerosis was pronounced, and the condition of the foreign body was unknown, the CFA was replaced by a 7 mm thin-walled, ringed, expanded polytetrafluoroethylene stretch graft. Microscopic examination of the material removed at surgery showed evidence of an amorphous foreign material consistent with remnants of the Angio-Seal together with multinucleated giant cells, which resulted from the foreign body reaction. The patient had an uncomplicated postoperative recovery. The ABI score improved to 0.68 for the right ankle, and the foot ulcer healed promptly.

## DISCUSSION

The Angio-Seal device is widely used for preventing bleeding and facilitating early ambulation after arterial puncture.[1,2] However, in terms of vascular complications, it remains controversial as to whether vascular closure devices are better than mechanical compression.[1–3] In addition, peculiar complications, such as stenosis, occlusion, and peripheral embolism, may arise from the use of an Angio-Seal device, it is necessary for clinicians to be aware of these complications.[3–8] Previous studies have reported that CFA occlusion due to the use of an Angio-Seal device occurred in 0.3% to 0.4% of the devices.[3,5]

Several possible mechanisms for the occlusion exist. The vessels were occluded because of the following factors: (i) the anchor of the device[4]; (ii) its collagen sponge, which had been unintentionally deployed in the arterial lumen[3, 6, 7]; (iii) a dissected plaque underneath the device[3, 4]; (iv) distal embolism caused by the device[6, 7]; (v) the intimal plaque lifted up by the anchor[5];

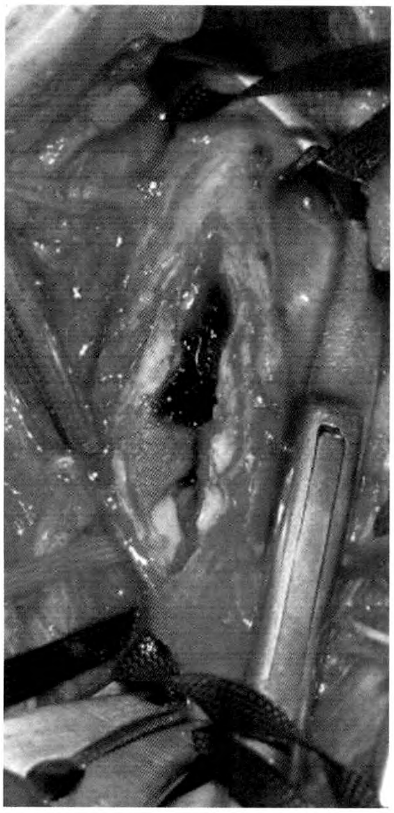

**Fig. 3** On surgical exploration, a pronounced fibrotic reaction was found surrounding the groin vessels. A collagen sponge with an attached thrombus was found in the CFA.

or (vi) massive periarterial and intra-arterial fibrosis.[4,8]

Abando et al. recommended against the use of the Angio-Seal device in cases in which the arterial puncture site is above the inguinal ligament or below the femoral bifurcation, or in cases involving small (<5 mm) arteries or heavily diseased arteries. In the present case, arteriosclerosis was very advanced even though the artery diameter was 6 mm.[5]

While most symptoms such as claudication or severe leg ischemia can appear within a few days, there are 2 reports of cases in which a delayed major complication was treated surgically. Wille et al. described a patient with leg ischemia that developed 37 days postprocedure[4]; Shaw et al. reported a case in which ischemic symptoms occurred in the patient 3 months after Angio-Seal implantation.[8] Here, we report the first case of a patient who developed a foot ulcer and underwent surgery 75 days after Angio-Seal implantation.

The Angio-Seal sponge is generally completely absorbed between 60 and 90 days after implantation. However, in our case, the gross appearance and microscopic evaluation confirmed that components of the Angio-Seal had not been absorbed and had incited a vigorous foreign body reaction; these factors together caused significant stenosis to the femoral artery, as was described in the report by Shaw et al.[8] Although uncommon, a patient may develop a vigorous foreign body reaction, resulting in failure of resorption.[4,8]

DUS can show the location and degree of atherosclerosis prior to puncture. In addition, the collagen sponge in the CFA was easily detected using DUS in our case. We recommend that both predeployment and postprocedure DUS should be performed to reduce the incidence of complications, especially in high-risk patients with small caliber (5–7 mm) and moderately calcified femoral arteries or patients with heavily diseased arteries.

Goyen et al. interventionally treated all 5 patients with Angio-Seal-associated occlusive complications.[6] However, percutaneous treatment is potentially associated with embolization and difficulty in removing large fragments of debris because they are fragile and not firmly attached to the vessel wall.[6,8] Therefore, in such cases, we believe that the best therapy is open surgical removal and repair of the artery. Since the extent and time course of bioabsorbability are not predictable, conservative treatment without removing the occluding material is not appropriate.

## CONCLUSION

In the present case, the Angio-Seal device had been deployed in the heavily diseased artery by a cardiologist at another hospital. This case highlights the fact that even if the size and position of the puncture site are good, the Angio-Seal device should be used while keeping in mind the occurrence of late occlusive complication; moreover, postprocedural monitoring after implantation is necessary, especially in the cases of severe arteriosclerosis.

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**Case Report**

# Simultaneous Endovascular Aneurysm Repair and Distal Gastrectomy in a Patient with Concomitant Abdominal Aortic Aneurysm and Advanced Gastric Cancer

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Katsuya Shimabukuro, MD, PhD, and Hirofumi Takemura, MD, PhD

**The optimal surgical management of patients with concomitant abdominal aortic aneurysm (AAA) and gastrointestinal malignancy remains controversial. A 79 year-old man who presented with hematemesis was found to have advanced gastric cancer concomitant with infrarenal AAA. The patient underwent simultaneous endovascular aneurysm repair (EVAR) and distal gastrectomy. The postoperative course was uneventful. The present case illustrates the clinical utility of EVAR for the high-risk patient with concomitant AAA and gastrointestinal malignancy.**

***Keywords:*** abdominal aortic aneurysm; endovascular aneurysm repair; gastric cancer

## INTRODUCTION

In recent years, the extended average life span has brought a high rate of malignancies associated with cardiovascular diseases. In particular, the incidence of gastrointestinal malignancies concomitant with abdominal aortic aneurysm (AAA) has also increased. Although cancer progression and aneurysmal rupture are both life-threatening events in patients with these clinical entities, current treatment strategy for this condition remains controversial.

We report a successful case of simultaneous endovascular aneurysm repair (EVAR) and distal gastrectomy for AAA and advanced gastric cancer.

## CASE REPORT

A 79 year-old man was admitted to a general hospital for the investigation of sudden hematemesis. He was noted to be suffering from general fatigue and appetite loss with 5 kg weight loss in a month. Upper gastrointestinal examination with contrast medium revealed a mass, 55 × 50 mm in size, on the anterior wall of the gastric antrum, and gastrointestinal fiberscopy showed a hemorrhagic tumor compatible with a Bormann type III gastric cancer, and the bleeding was successfully stopped with an endoscopic hemoclip (**Fig. 1**). He was given a blood transfusion and recovered smoothly. A biopsy specimen demonstrated moderately to poorly differentiated adenocarcinoma.

Computed tomography (CT) revealed a massive infrarenal AAA that measured 81 mm in maximum diameter (**Fig. 2A**). 3-dimensional computed tomography (3D-CT) showed the fusiform AAA with severe angulated proximal neck (**Fig. 2B**). We diagnosed the disease as advanced gastric cancer concomitant with AAA. Then he was referred to our institution for the operation of both lesions.

On physical examination, his conjunctivae were pale, but not icteric. A pulsating mass was palpated in his abdomen. Laboratory tests showed renal dysfunction with

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*Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

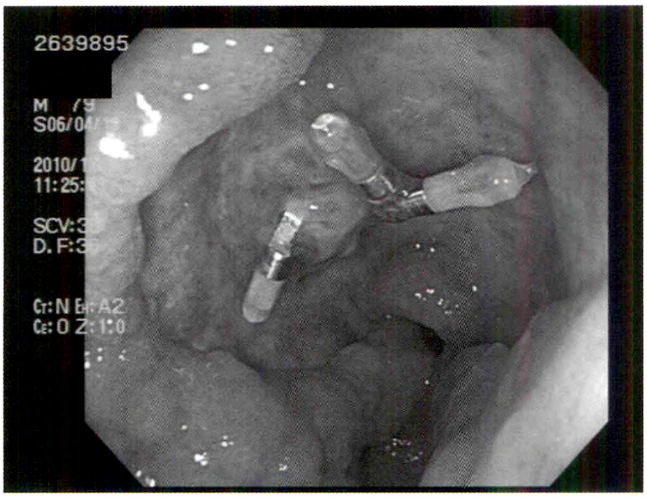

**Fig. 1** Gastrointestinal fiberscopy revealed a hemorrhagic tumor compatible with a Borrman type III gastric cancer on the anterior wall of the gastric antrum. The bleeding was successfully stopped with an endoscopic hemoclip.

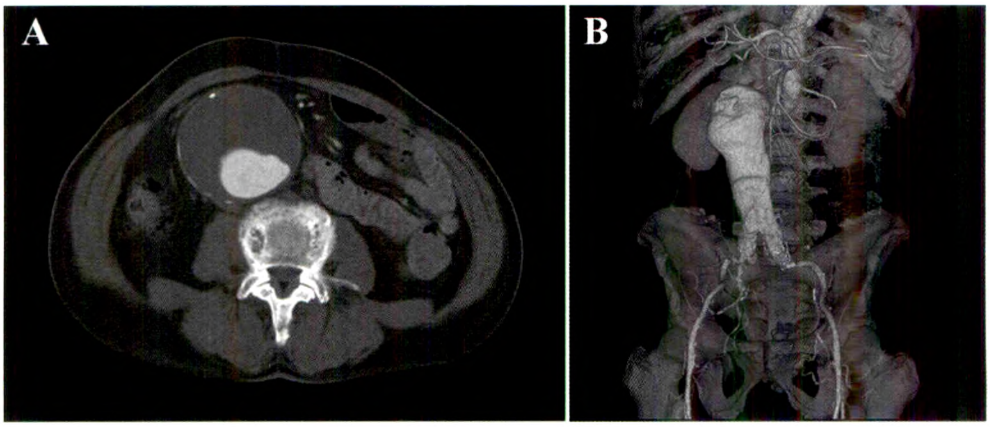

**Fig. 2** **A**: Contrast-enhanced computed tomography (CT) revealed a huge infrarenal abdominal aortic aneurysm (AAA) that measured 81 mm in maximum diameter.
**B**: 3-dimensional computed tomography (3D-CT) showed the fusiform AAA with a severe angulated proximal neck.

an elevated serum creatinine level (1.25 mg/dl). After we had discussed the surgical management including one or two-stage operation and open versus endovascular aneurysm repair (EVAR), we decided to perform the simultaneous EVAR and gastrectomy.

Under general anesthesia, bilateral common femoral arteries were exposed through inguinal incisions. A 28 × 12 mm × 18 cm bifurcated Gore-Tex (Excluder) stent graft was chosen. The main body of the system was inserted using through the left common femoral artery into the position just below the left renal artery. After optimal position was confirmed by aortography, the main body was deployed successfully. Then both graft limbs were deployed uneventfully. At the end, aortography confirmed type I endoleak. Therefore, a proximal aortic extension (aortic extender 28 × 30 mm), used to seal the angulated proximal neck, repaired the endoleak. Thereafter a median-laparotomy was performed. The gastric cancer invaded the transverse mesocolon and middle colic artery. A distal gastrectomy with systemic lymph node dissection was performed.

A postoperative 3D-CT on day 7 confirmed a patent endovascular graft in a good position without endoleaks (**Fig. 3**). The postoperative course was uneventful, and he was discharged on postoperative day 36.

## Discussion

Although the incidence of patients presenting with concomitant AAA and gastric cancer is low, current treatment strategies in patients with both lesions remains controversial.[1–4] The most important and difficult decision to make is whether to operate on the malignant lesion first, the AAA first, or both simultaneously. The decision-making may depend on many variables, including surgeon's experience and preference, local expertise, aneurysm size, and type and stage of cancer. As Szilagyi stated in 1967,[1] it is most important to assess the absolute indications for urgent surgical treatment of each lesion, being a high chance of aneurysm rupture, and such coexistent complications as hemorrhage, obstruction or perforation for the cancer. It is clear that the lesion which has the most dangerous complications should be operated on first.

The use of simultaneous operations for both lesions has several advantages. Risks accompanying total anesthesia, such as pneumonia or drug-induced complications, can be eliminated. Disease progression of the untreated lesion can be prevented. Surgeons have to keep in mind that there is a potential for aneurysm rupture if AAA resection is delayed by staged procedures. Furthermore, the anxiety of patients who are facing two life-threatening lesions is resolved at one time. On the other hand, the major disadvantage of simultaneous operation is the risk of prosthetic graft infection which may result in severe complications. In the present case, we selected the simultaneous operation because of the advanced hemorrhagic cancer and the high possibility of aneurysm rupture. We evaluated that the patient may be unable to tolerate a two-stage operation because of his advanced age and poor general condition.

The evolution of vascular endografts and the reported efficacy of EVAR provide an alternative method for treating complex and high-risk patients with acceptable mortality rate.[5–7] EVAR results in early recovery and a shorter convalescence compared with open graft replacement. This modality offers potential treatment benefits in patients with suitable anatomy who have concomitant gastrointestinal malignancy.[8–10] Herald et al. first reported the case of synchronous AAA and colorectal cancer treated entirely by minimally invasive surgery without laparotomy.[11] Since then, several reports have been described simultaneous EVAR and abdominal cancer resection.[12–14] However, almost all of those reports were undergoing a resection for colorectal cancer. While our present case was a high-risk gastric cancer patient complicated with AAA, so simultaneous EVAR and distal gastrectomy were performed, and a satisfactory outcome was obtained. EVAR should be considered the treatment of choice in high-risk patients, taking into account, however, that this treatment is not always feasible in all cases and that in patients with a normal life-expectancy it may not always be the right choice. Thus, a preoperative evaluation including a psychiatric assessment, especially in aged patients, should be carefully conducted when selecting the appropriate surgical procedure.

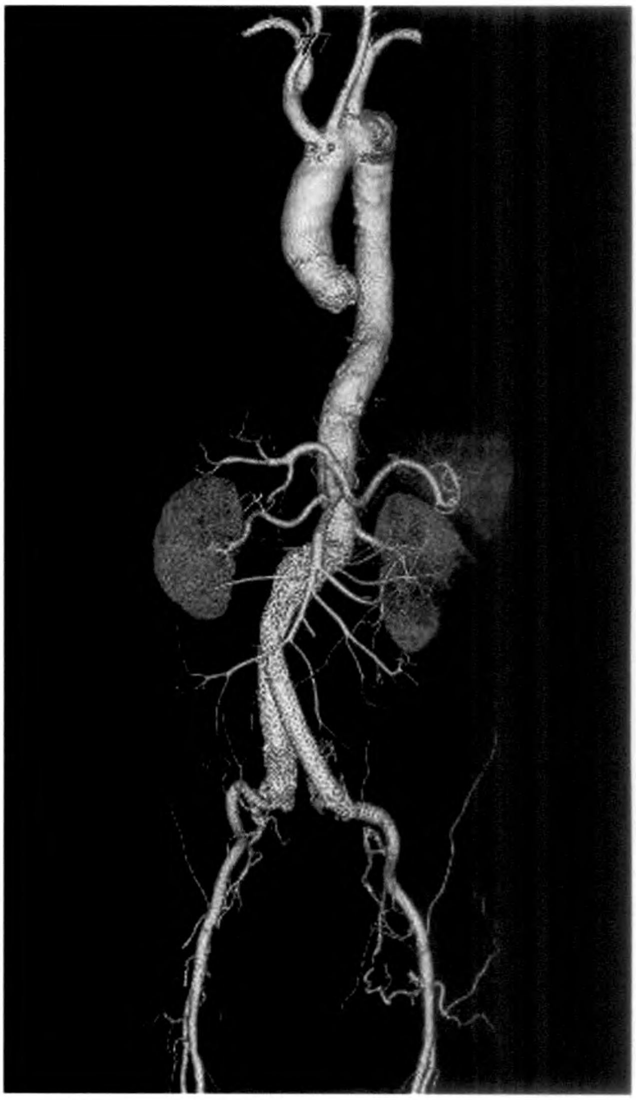

**Fig. 3** Postoperative 3D-CT confirmed a patent endovascular graft in a good position without endoleaks.

In conclusion, we successfully performed simultaneous EVAR and distal gastrectomy in a patient with concomitant AAA and advanced gastric cancer. EVAR is a safe and effective treatment for high-risk patients with a relatively low procedure-related morbidity and no mortality.

## DISCLOSURE STATEMENT

The authors declare that they have no competing interests.

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**Case Report**

# Preservation of Aortic Arch Branches Using Chimney and Sandwich Stent Grafts

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and Shigeki Higashi, MD, PhD[2]

***Purpose:*** **To share our hybrid endovascular experiences using chimney or sandwich stent grafts for acute aortic arch pathologies.**

***Methods:*** **Hybrid procedures for a distal aortic arch aneurysm and an ascending anastomotic aortic aneurysm rupture were reported. Right to left common carotid and left axillar artery bypasses were located. Covered stents were inserted into the inominate artery, with the flow-proximal end located in the ascending (standard chimney) or the descending aortic stent graft (retrograde sandwich).**

***Results:*** **Both cases had no signs of brain ischemia. Aneurysms are decreasing in size.**

***Conclusion:*** **Chimney and sandwich techniques were technically feasible in the complex and acute situations.**

***Keywords:*** carotid artery bypass; retrograde sandwich; covered stent

## INTRODUCTION

Endovascular stent graft was introduced as a less invasive treatment for the cases intolerant with conventional surgical treatment. However, the cases with unfavorable anatomical factors are empirically more unfit to surgical procedures. The surgical procedures increase the technical difficulty and invasiveness, related to the preservation of blood circulation of aortic branches. With the advent of endovascular techniques, management of aortic branches has thus come into sharp focus. Fenestrated or branched stent-graft techniques may cast a light on the future treatment of such complicated cases.[1)] Unfortunately, such devices cannot be used in acute situations, since they have to be customized and fabricated to fit the case-specific anatomy. The purpose of this report is to share our endovascular experiences of chimney or sandwich technique for the treatment of acute and complex aortic arch pathologies.

## CASE REPORTS

### Rapidly expanding distal aortic arch aneurysm

The patient was a 76 year-old male, who had acute myocardial infarction (MI) in the left main coronary arterial area. The saccular aneurysm with the maximum diameter supersizing 6 cm was detected during the hospital stay, which expanded to 8 cm in a month. Mainly because of the recent MI and an increased level of serum creatinine (210 μmol/L), conventional arch repair (logistic Euroscore = 13.19, Japan score = 21.1) was considered unsuitable, and the patient was referred to us for an endovascular solution. A right common carotid (CCA) -left CCA -left axillar artery (LAxA) bypass was created using a 6 mm of Dacron graft (Gelsoft ERS, Terumo, Tokyo, Japan), lead through the retropharyngeal space and costoclaviclar passage. A thoracic stent graft (40 mm × 15 cm, Gore TAG Thoracic Endoprothesis, W.L. Gore & Associates, Flagstaff, AZ) was introduced from the right common femoral artery

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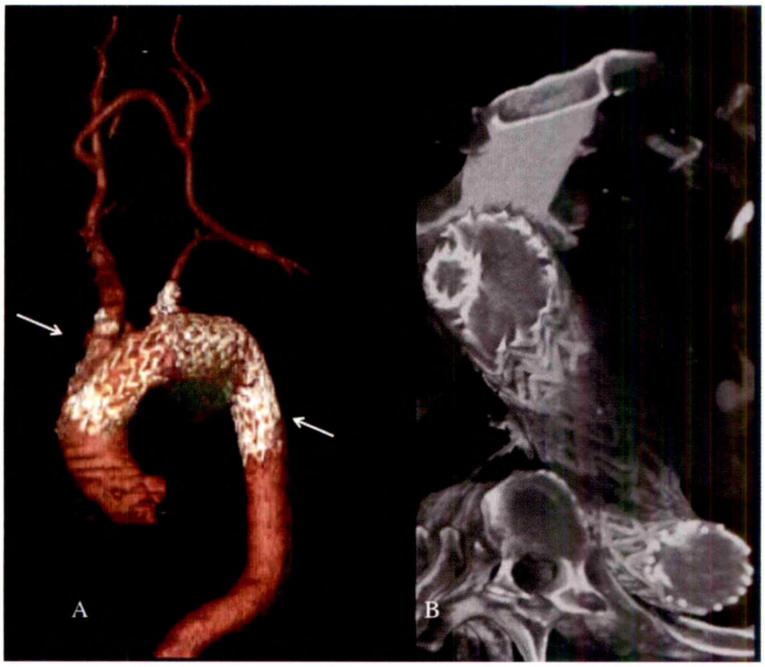

**Fig.1** **A**: Three dimensional CT angiography. The green area indicates excluded aneurysm. Arrows indicate the level of tilted plane above which the volume data was rendered as in **B**: Partial volume rendering image. Note deformation of the upper surface of the aortic stent graft. A w-shaped curve was formed so that it covered the aortic endoluminal surface of the covered stent.

(RCFA) with the proximal end located in the ascending aorta. As a "chimney" stent graft, an ancillary component of an abdominal aortic endograft (14.5 mm × 7 cm, iliac leg extension of Gore Excluder AAA Endoprothesis, W.L. Gore & Associates, Flagstaff, Az) was used to preserve the circulation of INA. Aortic and branch stent grafts were inflated carefully. A keen attention was utilized to avoid the aortic injury, which may be caused by an over expansion due to the balloons located in the parallel position. Left subclavian artery (LSA) was coil-embolized with platinum-tungsten coils (Interlock fibered IDC occlusion system, Boston Scientific Corporation, Boston, MA). A final angiogram found no signs of endoleak. The patient tolerated the whole procedure, and showed no signs of ischemic stroke postoperatively. Three-dimensional CT at the 12th postoperative month found no signs of endoleak and a marked reduction of aneurismal diameter (**Fig. 1**).

### Ascending aortic anastomotic rupture

The patient was a 79 year-old female, who had a previous surgical history of ascending aortic grafting for acute aortic dissection five years ago, and omentum patch thereafter for the postoperative dehiscence of median sternotomy. Computed tomography, performed for acute chest discomfort, revealed chronic and contained rupture of the ascending anastomotic aortic aneurysm rupture (**Fig. 2**). A right CCA-left CCA-LAxA bypass was created as aforementioned. Because of the flexion in the ascending aortic graft, the proximal insertion of chimney stent graft was considered hazardous to get a proximal endoseal. The first (distal) thoracic stent graft (34 mm × 15 cm, Gore TAG Thoracic Endoprothesis, W.L. Gore & Associates, Flagstaff, AZ) was delivered through the RCFA, and located with the proximal end located about five millimeters distally to the opening of the inominate artery (INA). A covered stent (14.5 mm, iliac leg extension of Gore Excluder AAA Endoprothesis, W. L. Gore & Associates, Flagstaff, Az) was delivered from the INA into the endolumen of distal thoracic stent graft in the descending aorta. The proximal thoracic stent graft (34 mm ×15 cm) was deployed with the proximal end located inside the previous ascending graft. The distal end of the second (proximal) stent graft was located, so that 6 cm of the covered stent for the INA was held (i.e.,

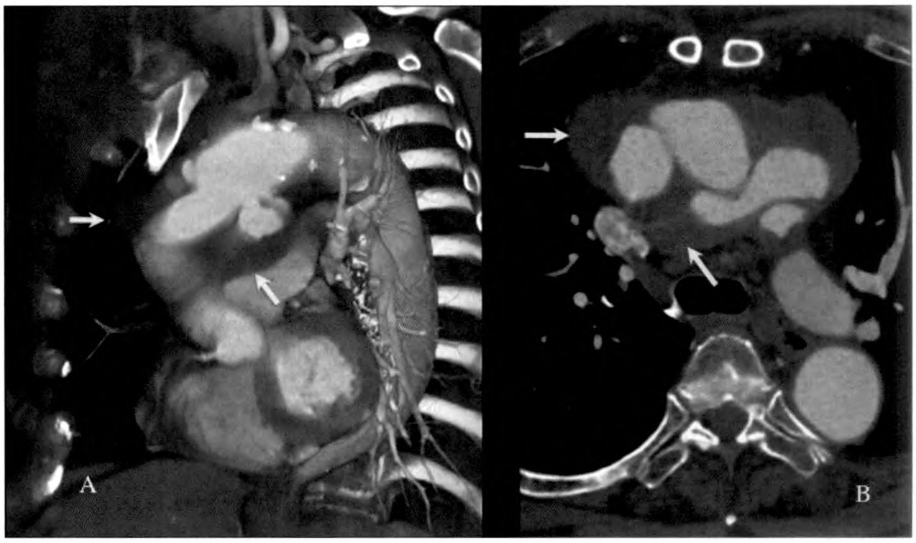

**Fig. 2** Partial volume rendering (**A**) and axial images (**B**) of the preoperative computed tomography were shown. Arrows indicated the anastomotic aneurysm and widespread thrombus near the proximal anastomosis.

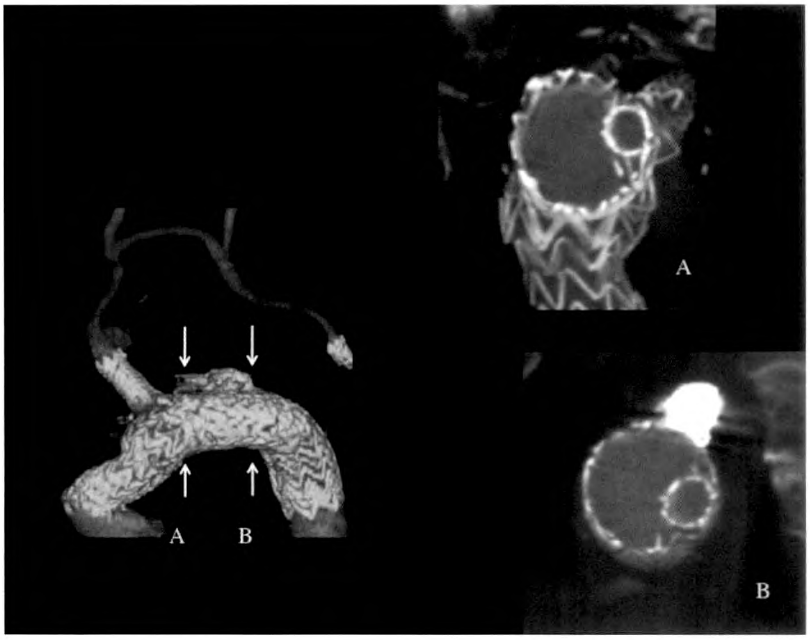

**Fig. 3** Postoperative CT angiography.
Arrows in the left figure indicate the level of tilted plane above which the volume data was rendered as in the levels **A** and **B**. The covered stent was tightly sandwiched.

sandwiched) between the second and first (distal) stent grafts. Completion angiography recognized no sign of endoleak. The INA stent graft was "sandwiched" by the distal and proximal aortic stent grafts (**Fig. 3**). Postoperative CT found a marked reduction of excluded volume of aneurysm or thrombus (**Fig. 4**).

## DISCUSSION

Greenberg had reported that the proximal landing zone could be extended above the ostium of renal arteries by deploying a self-expanding stent into the renal artery with a segment of the stent running parallel to the aortic wall

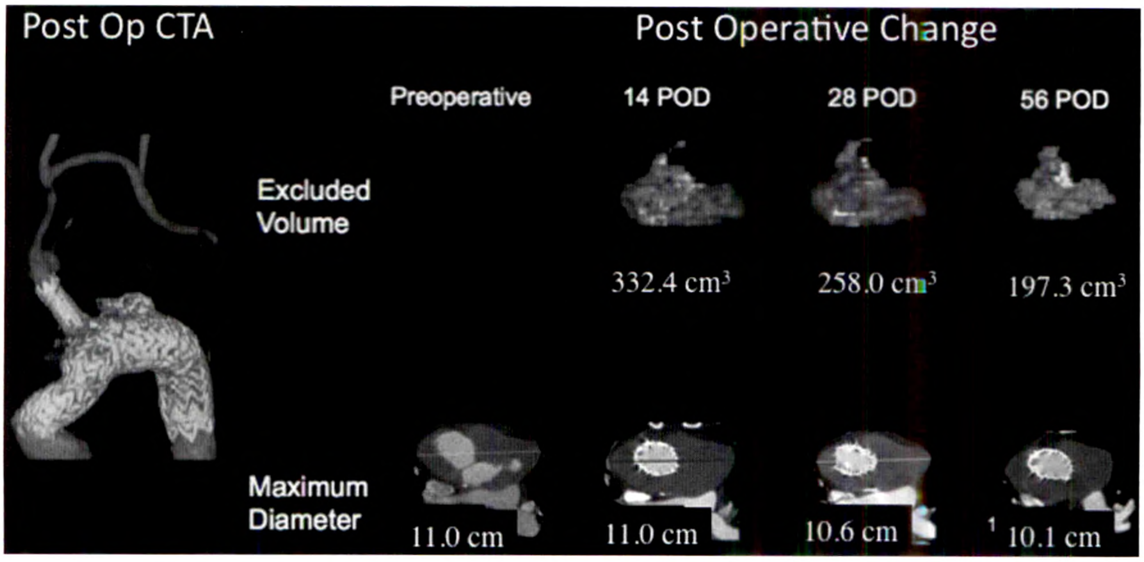

**Fig. 4** Volumetric analysis of excluded aneurysm.
Postoperative CT angiography found a marked reduction of excluded aneurysm or thrombus.

and the main stent graft.[2)] In the territory of arch vessels, Larzon introduced "top fenestrated technique," wherein the circulation into LCA and left subclavian arteries were maintained similarly.[3)] Ohrlander proposed the term "chimney graft" when covered stents were employed in a similar fashion.[4)] Allaqaband has described another concept, the "sandwich technique," which consists of one or more covered stents from inside of the previously deployed aortic stent graft into the target vessel(s). It obtains an endo-seal by deploying the next aortic stent graft inside, with the proximal opening of covered stent(s) uncovered.[5)]

"Chimney" and "sandwich" stent-graft techniques have some issues for consideration. One problem is a type I or III endoleak caused by branch stent grafts extending through the proximal and distal sealing zones. Theoretically, the more the branch stent grafts are used, the greater the potential for the leak. The longer the overlap zones are, the less likely the leak would be detected. In our literature search, maximally two stents per each proximal or distal aortic sealing zone were inserted, and the overwrap zones seemed to be longer than 3 cm for the chimney stent graft and longer than 6 cm for the sandwich. The numbers of branch stent grafts could be reduced by the aforementioned surgical procedures. Blood supply into the stent grafts for the arch branches should be also considered. In the latter case, the stent graft into the INA was inserted so that the blood flow is delivered in the way opposite to the aortic main flow. We had concerned the adequacy of flow volume supplied in this fashion and had prepared the RCFA-RCA bypass. However, during this procedure, there was no significant decrease of brain oxygenation measured by photospectroscopy, and the case experienced no ischemic complications. No reports about the use of sandwich technique in combination to carotid arterial reconstruction, where the innominate arterial flow is reversely supplied, could be hitherto found in our literature search.

In the extra-anatomical bypass for these cases, the selection of proximal/distal anastomosis is an issue for considerations. In carotid arterial procedures, ischemic complications are mostly caused by the brain emboli.[6)] As we are aware of this issue, we selected cervical portion of common carotid arteries for the anastomosis of bypass grafts, where the deposition of atheromatous debris is less likely. If severe degree of brain ischemia is detected, usage of any form of arterial shunt could mitigate the degree of brain ischemia.[7)] Furthermore, durability and patency of chimney and sandwiched stent grafts should be monitored carefully, because these were under the influence of other stent grafts. It should be also reminded that long term patency of the extra-anatomical bypass could not be guaranteed. In addition, the case with atheromatous diseases in carotid arteries or INA, indication of aforementioned techniques should be carefully decided.

In summary, so-called chimney or sandwich stent grafts seemed feasible for the treatment of acute and complex aortic arch pathologies. These techniques inherently have the risk of damaging aortic sealing in their passages, and may have other case-specific problems. These problems would not be fully solved, but might be partially mitigated by current devices and techniques.

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**Case Report**

# Iatrogenic Acute Aortic Dissection during Percutaneous Coronary Intervention for Acute Myocardial Infarction

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**Iatrogenic acute aortic dissection during percutaneous coronary intervention is an extremely rare, but critical complication. Localized aortic dissections have been treated by sealing the entry with a coronary stent. Extensive dissections may require a surgical intervention. We present a case of type A extensive aortic dissection occurring during angioplasty of the left circumflex artery for acute myocardial infarction. This iatrogenic aortic dissection required emergent surgical repair with supracoronary replacement of the ascending aorta.**

***Keywords:*** iatrogenic acute aortic dissection, percutaneous coronary intervention, acute myocardial infarction

## INTRODUCTION

Acute aortic dissection is a life-threatening event that requires early recognition and frequently requires emergent surgical treatment. It usually occurs spontaneously in patients with long-standing hypertension and cystic medial necrosis of the aortic wall. The occurrence of dissection of the ascending aorta as a complication of coronary angiography or coronary angioplasty is exceedingly rare.[1] In contrast, coronary dissection is a well-known complication of coronary angioplasty that nowadays can be successfully treated with intracoronary stenting.

The options for treatment are determined on the basis of patient stability, nature of dissection of the coronary artery, and extent of aortic dissection. Surgical intervention is associated with particularly high risk in unstable patients with acute myocardial infarction (AMI). We present a case of a patient who developed an iatrogenic acute aortic dissection during percutaneous coronary intervention (PCI) following an AMI.

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## CASE REPORT

A 66 year-old man with untreated hypertension was admitted to our hospital because of AMI. The patient's blood pressure was 140/60 mmHg on admission. An electrocardiogram showed elevation of the ST segment in II, III, and aVf leads. Serial creatine kinase levels were elevated at 3065 U/L (normal range, 25–195 U/L). A coronary angiography (CAG) using a MP 3.75 4Fr guide catheter, performed through the right radial artery approach, revealed single vessel disease with a 100% proximal left circumflex artery (LCX) lesion (**Fig. 1**). When we carried a Launcher EBU 3.5 6Fr guide catheter, there was resistance with the brachiocephalic artery and the patient complained of the right shoulder pain. However, reperfusion was achieved by passing a guidewire (Rinato) through the affected artery, followed by aspiration thrombectomy. After balloon predilatation of the LCX lesion, a bare metal stent (3.5–18 mm DRIVER, Medtronic) was implanted. An angiogram showed antegrade thrombolysis in myocardial infarction (TIMI) 3 flow in the LCX. During coronary angioplasty, the patient's blood pressure was normal range. After coronary intervention, the patient developed retrosternal pain and complained of a migrating pain starting in the neck to the back. At this point, we noticed this critical complication. In preparations for an emergent CT scan, the patient's blood pressure dropped (60/40 mmHg), and he required rapid fluid replacement.

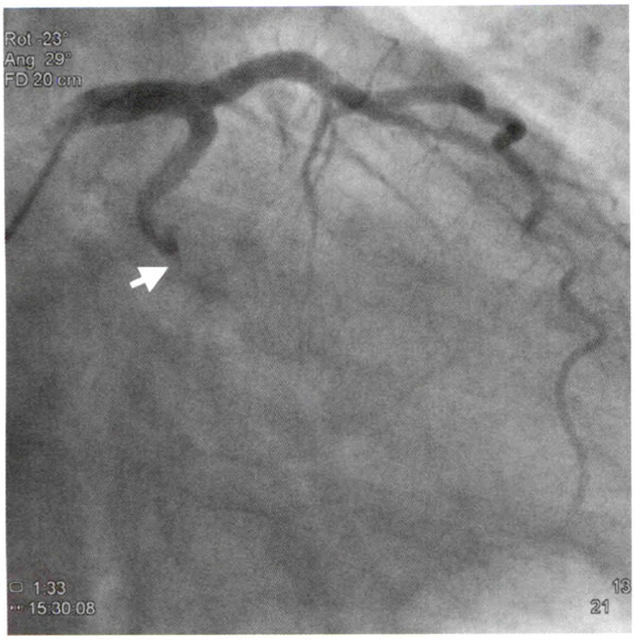

**Fig. 1** Diagnostic coronary angiogram showing a 100% lesion in the proximal left circumflex artery (arrow).

Transthoracic echocardiography showed a large quantity of pericardial effusion. An emergent CT scan revealed an extended aortic dissection from the ascending aorta to the abdominal aorta (**Fig. 2a**).

An emergency operation was performed because of hemodynamic deterioration. Cardiopulmonary bypass was immediately established by right femoral artery and bicaval cannulation, and the patient's body was cooled. The ascending aorta was dilated to as much as 4.5 cm in diameter and was a dark reddish color along its entire length. Because the CT-Scan revealed intimal tear around the brachiocephalic artery, the aortic cross-clamp was not performed. Hypothermic circulatory arrest was induced at 22°C, and the ascending aorta was opened. For myocardial protection, cold blood cardioplegic solution was administered retrogradely through the coronary sinus. Careful observation revealed no intimal tear in the proximal or around the left coronary orifice. The initial entry of dissection was located at the front of the ascending aorta near the orifice of the brachiocephalic artery. Moreover, the size of entry was approximately 3 cm. After the entry abscission, the ascending aorta was reconstructed with a 26-mm woven Dacron graft (**Fig. 2b**). The patient was weaned from cardiopulmonary bypass without difficulty. He recovered uneventfully and was discharged on the 16th postoperative day.

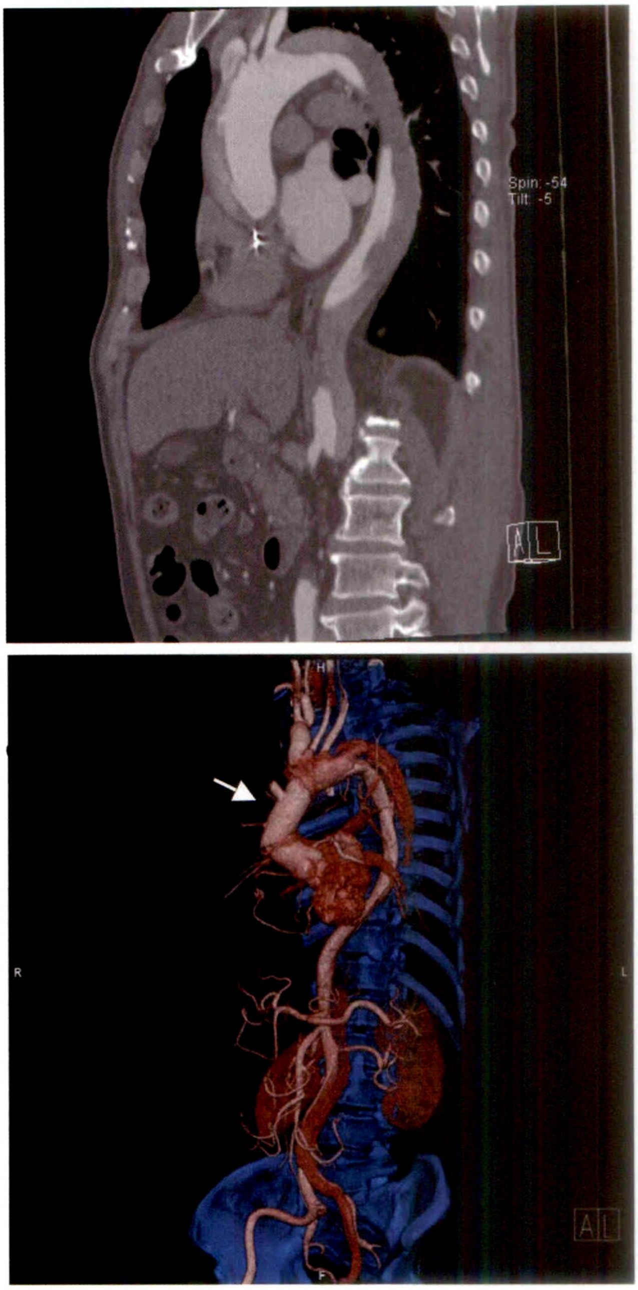

**Fig. 2** **a**: Computed tomography scan immediately after PCI showing a dissection of the thoracic aorta.
**b**: Computed tomography scan 2 weeks after replacement of the ascending aorta (arrow).

## DISCUSSION

Acute aortic dissection during cardiac catheterization is a very rare complication. (overall incidence, 0.02%) and occurs more frequently in the emergency setting of AMI (0.19%) than in an elective setting (0.01%).[2] The incidence is generally higher during PCI (overall 0.03%) than during diagnostic procedures (<0.01% in elective settings).[2)]

In most previously reported cases, the entry point was within a dissected coronary artery with progressive retrograde dispersion within the subintimal space in the aortic root. Few studies have reported isolated dissection of the aorta without involvement of coronary arteries.[3)] In our case, the entry point was located around the brachiocephalic artery, and the coronary artery was not dissected.

The etiology of this condition is most likely multifactorial. Several possible mechanisms have been proposed: retrograde propagation of a coronary dissection resulting from mechanical trauma due to a wire, catheter, inflated balloon, or other device and aortic trauma resulting directly from the guide catheter.[4)] The nature of the coronary lesion to be treated may have the greatest impact on the probability of aortic dissection occurring because of catheterization. Heavily calcified vessels, which often require more aggressive guiding catheter manipulation in order to deliver coronary balloons and stents, are inherently more prone to dissection.[5)]

In recent years, a transradial approach has gained widespread acceptance among interventional cardiologists, aiming to minimize bleeding complications and increase patient comfort. However, technical failure has been reported up to 5% of cases even if performed by skilled operators. The main reason of failure is represented by anatomic abnormalities of upper limb arteries and subclavian-brachiocephalic axis.[6)] We postulate that the cause of the aortic dissection in our patient was an aggressive manipulation of the guiding catheter through the right radial artery approach, given that the intimal tear was located around the brachiocephalic artery. Moreover, we assume that an aggressive manipulation probably occurred because of presence of anatomic abnormalities of subclavian-brachiocephalic axis. Next, we consider the management of catheter-induced aortocoronary dissection. Dunning and colleagues[7)] have classified aortocoronary dissection based upon the extent of aortic involvement: Class I, contrast staining involves only the coronary cusp; Class II, contrast extends up the aortic wall to <40 mm; and Class III, contrast extends to >40 mm up the aortic wall. In their published case series, the extent of propagation of aortic dissection yielded prognostic information, with Class III dissections having uniformly poor outcomes. This classification may be useful for risk stratification. The optimal treatment for this complication has not been established, but it had been recommended that cases of localized aortocoronary dissection not complicated by ischemia or hemodynamic instability can be treated with intracoronary stenting or conservative management. However, if ischemia of any of the aortic branches occurs, or if there is extensive dissection or hemodynamic instability, urgent surgery is the treatment of choice.[8)]

In our patient, the iatrogenic aortic dissection occurred during PCI for AMI and was very extensive. Moreover, the patient also experienced hemodynamic deterioration due to cardiac tamponade, and emergent surgery was required in spite of a high risk. Lentini and Perrotta[9)] suggest that despite considerable myocardial protection and improved surgical techniques, the mortality rate for patients with aortic dissection complicated by extensive myocardial damage remain high. The patient's serial creatine kinase levels increased to 3065 U/L before emergent surgery. It was therefore assumed that the operative mortality of replacement of the ascending aorta was very high because of the poor cardiac condition and severe inflammatory response. In conclusion, this case demonstrates an iatrogenic acute aortic dissection with a supracoronary entry without involvement of the coronary arteries, which most likely occurred as a result of rather aggressive use of a guide catheter. Fortunately, this patient recovered well after emergency replacement of the supracoronary ascending aorta. However, this complication is extremely dangerous and is a life-threatening event; therefore, it is crucial to prevent a catheter-induced aortic dissection during PCI. In particular, the operator should be aware of the possibility of dissection during aggressive manipulation of guide catheters.

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**Case Report**

# Intrathoracic Left Subclavian Artery Aneurysm: Report of a Case

Tetsuya Niino, MD, Satoshi Unosawa, MD, and Kazuma Shimura, MD

**Aneurysms of the intrathoracic subclavian artery are extremely rare. A 74 year-old man was referred to our hospital with an abnormal chest X-ray film. Contrast computed tomography revealed an intrathoracic left subclavian artery aneurysm. Via left 4th posterolateral thoracotomy, the aneurysm was exposed under systemic deep hypothermia and circulatory arrest. The distal arch was replaced with a 26 mm single-branched graft and the left subclavian artery was reconstructed with a 10 mm graft.**

***Keywords:*** subclavian artery, aneurysm, surgery

## INTRODUCTION

Subclavian artery aneurysm (SAA) is a rare peripheral aneurysm. The most common causes of true SAA are atherosclerosis, thoracic outlet syndrome, infection, trauma, and congenital arterial anomalies such as Marfan syndrome or von Recklinghausen's disease.[1] These aneurysms can undergo rupture, thrombosis, or embolism, and can cause symptoms by local compression. Here, we present our experience with an aneurysm of the intrathoracic left subclavian artery.

## CASE REPORT

A 74 year-old man was referred to our institution after an abnormality was detected on his chest X-ray film (**Fig. 1**). Physical examination was unremarkable. The blood pressure was normal and equal in both upper extremities (120/80 mmHg). He had no history of trauma, infection, congenital arterial anomalies, or systemic vasculitis. Computed tomography (CT) demonstrated an aneurysm that measured 3.9 cm on the proximal part of the left subclavian artery. There were no other aneurysms. CT also revealed dilatation of the ostium of the left subclavian artery (**Fig. 2**). The aneurysm increased from 3.9 cm to 4.9 cm in diameter after 11 months on repeat CT (**Fig. 3**). The patient was anxious about the aneurysm and requested graft replacement.

The operation was done via left posterolateral thoracotomy through the 4th intercostal space. After systemic heparinization, the right femoral artery and femoral vein were cannulated, and cardiopulmonary bypass was established. The aneurysm was exposed under systemic deep hypothermia and circulatory arrest. The distal arch was replaced with a 26 mm single-branched graft (Triplex, Terumo Co., Tokyo, Japan) and the left subclavian artery was reconstructed with a 10 mm graft. Operative findings confirmed that the aneurysm was due to atherosclerosis and not trauma.

His postoperative course was uneventful, and follow-up CT confirmed a good result (**Fig. 4**).

## DISCUSSION

Aneurysms of the subclavian artery are infrequent, accounting for less than 1% of atherosclerotic aneurysms in a large series.[1] The most common etiology of aneurysms at this location is atherosclerosis, followed by infection, Marfan syndrome, and thoracic outlet syndrome.[2]

SAA can sometimes be completely asymptomatic, as in the present case. When symptoms occur, chest pain or

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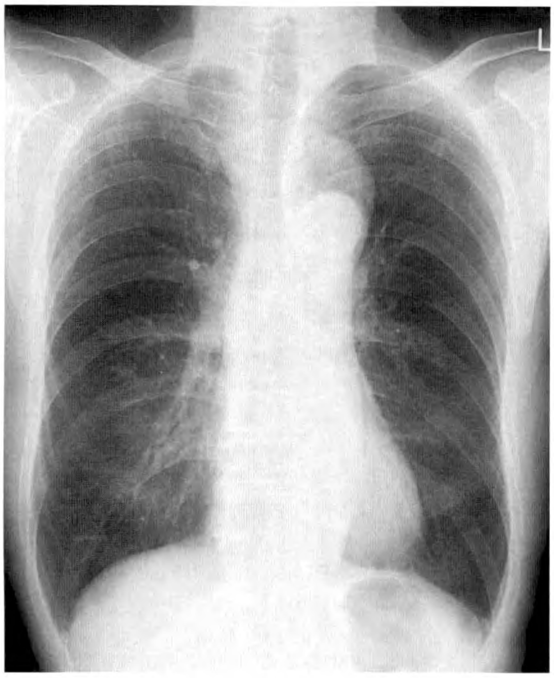

**Fig. 1** Preoperative chest X-ray film shows a left mediastinal mass.

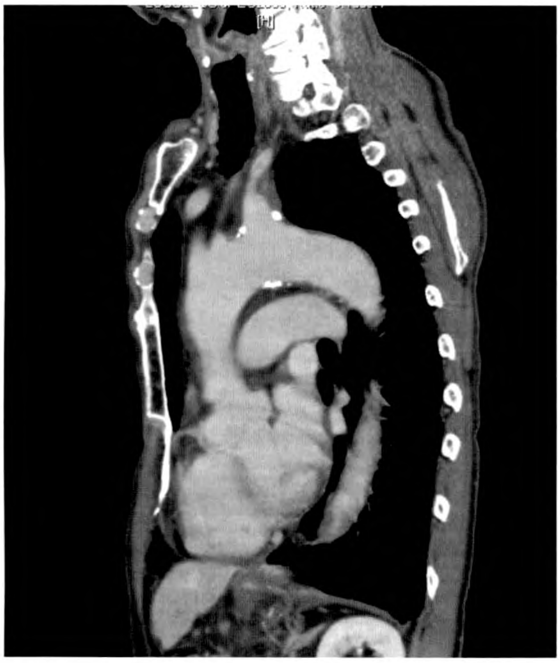

**Fig. 2** Contrast-enhanced CT scan showing the dilated ostium of the left subclavian artery.

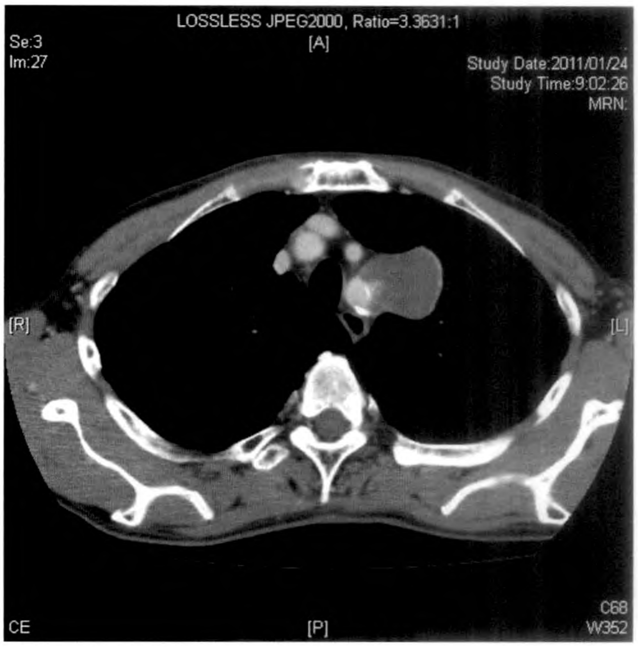

**Fig. 3** Contrast-enhanced CT scan showing an aneurysm of the left subclavian artery.

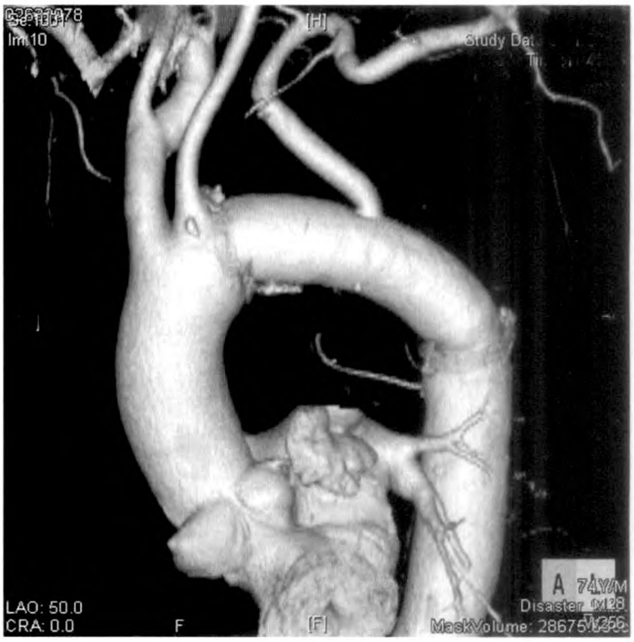

**Fig. 4** Multislice CT at 2 months postoperatively.

shoulder pain is most common. SAA can undergo rupture, thrombosis, or embolism, and can cause symptoms due to local compression.

The natural history of SAA is unknown. However, a high incidence of death from rupture and exsanguination has been reported regardless of the size of the aneurysm.[3] Therefore, an aggressive approach must be taken when dealing with SAA. It has been reported that the operative mortality rate for SAA repair is 6%, with a morbidity rate of 25%.[4)] In patients with atherosclerotic aneurysms, it is important to rule out other aneurysms elsewhere in the body since the incidence of associated aneurysms ranges from 33% to 47% and a significant number of late deaths from rupture of such aneurysms has been noted.[4)]

In many patients with a proximal left SAA, the orifice of the subclavian artery is fragile and dilated, so reconstruction by anastomosis or direct closure of the artery with a patch graft is difficult.[2)] The best approach for proximal left SAA remains controversial. It has been conventional to approach the intrathoracic left subclavian artery through a left 4th intercostal posterolateral thoracotomy in order to obtain proximal control, but median sternotomy has also been employed.[5)] However, the left subclavian arteries arises from the distal arch of the aorta and lies posteriorly in the thoracic cavity, sometimes making it difficult to obtain distal side of subclavian artery control via an anterior approach, in these cases the posterolateral approach is considered to be useful.

Surgery is the main treatment for SAA, and endoluminal stent grafting may be the method of choice for high-risk surgical candidates.[2)] On the other hand, endovascular repair of intrathoracic left subclavian artery aneurysm and total endovascular debranching of the aortic arch have recently been reported.[6,7)] Endovascular aortic repair may be an alternative to conventional surgical repair for patients with left SAA.

In conclusion, we reported a 74 year-old man in whom we treated an atherosclerotic aneurysm of the intrathoracic left subclavian artery.

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**Case Report**

# Endovascular Stenting for Left Subclavian Venous Stenosis for a Hemodialysis Patient with a Persistent Left Superior Vena Cava

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**A persistent left superior vena cava (PLSVC) is the most common thoracic venous anomaly, and we should be aware of its existence. We encountered a case of significant left arm swelling due to recurrent left subclavian venous stenosis in a hemodialysis patient with a PLSVC. Endovascular stent placement was performed safely and effectively for the stenosis employing the pull-through technique, in which a guidewire was passed from the left internal jugular vein to the access vein. On the following day, left arm swelling had improved. 3 months after stent placement the left arm swelling has not recurred.**

***Keywords:*** stent, pull-through technique, persistent left superior vena cava

## INTRODUCTION

The prevalence of a persistent left superior vena cava (PLSVC) is estimated to be approximately 0.3%–0.5% in individuals with a normal heart and 4% in those with congenital heart disease.1) A PLSVC can be detected incidentally during procedures such as hemodialysis (HD) catheter placement,2,3) and can cause difficulties during central venous and pulmonary artery catheterization.4) Serious complications such as shock, angina and cardiac arrest have been described during catheterization in adults with a PLSVC.5,6)

Recently, we encountered a recurrent left subclavian venous stenosis in an HD patient with a PLSVC. We performed endovascular stent placement safely and effectively for the stenosis employing the pull-through technique from the left internal jugular vein to the access vein.

## CASE REPORT

The patient was a 56 year-old man who had undergone HD due to renal failure following chronic glomerulonephritis for 28 years. The patient presented with left arm swelling 1 year after new creation of a native brachial arteriovenous (A-V) fistula for HD. Percutaneous transluminal angioplasty (PTA) for the stenosis of the left subclavian vein was performed twice within 2 months at another hospital. However, arm swelling recurred a few weeks after the last PTA, and then the symptoms gradually worsened. The patient did not want closure of the A-V fistula. Therefore, he was referred to our hospital for endovascular stent placement. At the time of hospital admission, the patient had left upper arm and forearm diameters of 31 and 25 cm.

Initially, the access vein was punctured with an 18 gauge needle. Then, venography, obtained by the manual injection of 12 mL of contrast medium (150 mg of iodine

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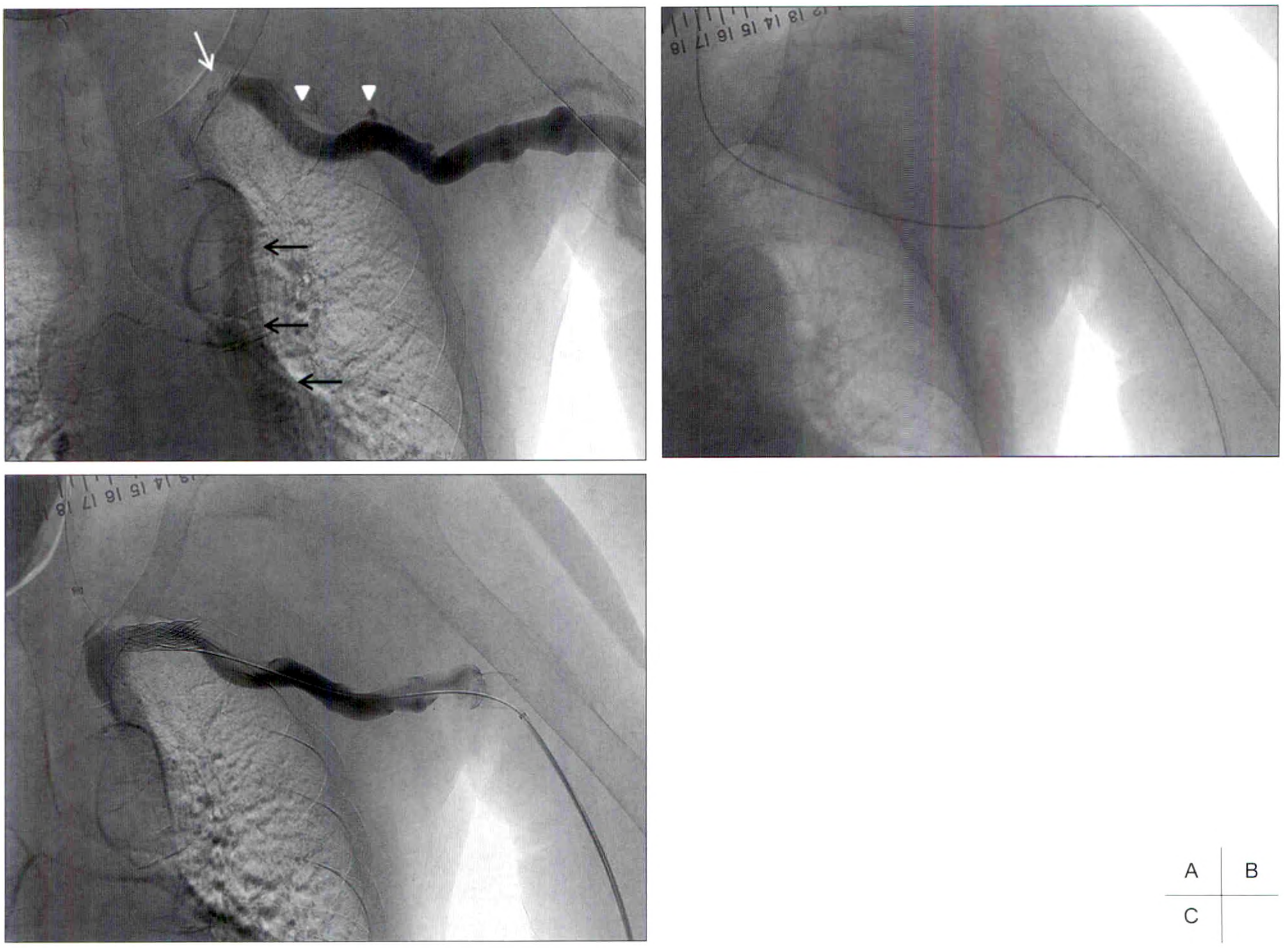

**Fig. 1** **A**: Venography demonstrated a persistent left superior vena cava (arrows), severe focal stenosis of the left subclavian vein (white arrow), and development of collateral veins (arrowheads).
**B**: After the insertion of a sheath introducer from the left jugular vein, a 0.035-inch guidewire was pulled through with the sheath from the access vein.
**C**: A stent was precisely deployed over the stenotic lesion without protrusion into the persistent left superior vena cava. Additionally, the venography revealed resolution of the subclavian venous stenosis and disappearance of collateral veins.

per milliliter) with an 18 gauge needle, revealed a PLSVC and focal severe stenosis of the left subclavian vein (**Fig. 1A**). The diameter of the adjacent vein was approximately 12 mm.

The patient received an intravenous heparin injection of 3000 U (50 U/kg) before the procedure. After the insertion of a 7-French sheath introducer from the puncture site under local anesthesia, the stenosis was traversed with a hydrophilic 0.035-inch guidewire (Terumo, Tokyo, Japan) and a 5-French catheter (Clinical Supply, Gifu, Japan) through the sheath introducer. A balloon catheter of 8 mm in diameter and 20 mm in length (Powerflex; Cordis, Miami, FL, USA) was inserted through the sheath introducer and inflated over the stenotic lesion at 10 atm for 1 minute as pre-dilatation. Then, we performed stent placement. The diameter of the adjacent vein was so large that there was a possibility that the stent would migrate to the PLSVC. To prevent such migration and provide sufficient traction to deliver a large-sized catheter device, we decided to place the stent employing the pull-through technique as follows. First, a 7-French sheath introducer was inserted from the left jugular vein under local anesthesia. Next, a 0.035-inch guidewire of 260 cm in length (Terumo) was inserted through a 5-French catheter which was advanced through the 7-French sheath introducer placed in the left jugular vein. The 0.035-inch guidewire was navigated into the sheath from the access vein. The guidewire was grasped by surgical forceps with the sheath inserted from the access vein and was pulled out of the sheath (**Fig. 1B**). Then, the 5-French catheter was withdrawn. The 7-French sheath inserted from the left jugular vein was exchanged with a 12-French stent delivery sheath of 60 cm in length (GZVI; COOK, Bloomington, IN, USA). Finally, a 10 to 25-mm diameter and 30.6 to 39.0-mm-long Palmaz XL stent (Cordis), mounted over a balloon catheter of 15 mm in diameter and 40 mm in length (Maxi-LD; Cordis), was precisely deployed without protrusion into the PLSVC via the 12-French sheath after stenotic lesion coverage became optimal on venography (**Fig. 1C**). During advancement of the stent mounted over the balloon catheter, tension was maintained at both ends of the 0.035-inch guidewire. On the following day, left arm swelling had improved (diameter of the left upper arm and forearm were 27 and 19 cm, respectively), and the patient was discharged from the hospital. Post-procedural anticoagulation or antiplatelet therapy was not prescribed.

3 months after stent placement the left arm swelling has not recurred.

## DISCUSSION

The PLSVC descends vertically in front of the aortic arch, close to and slightly lateral to the vagus nerve, and, in most cases, enters the right atrium by way of the coronary sinus.7) Catheter tip manipulation in the coronary sinus may cause serious complications such as shock, cardiac arrest, and angina in adults with a PLSVC.5)

Central venous stenosis or occlusion is a common complication that leads to access dysfunction in HD patients. Endovascular treatment for central venous stenosis or occlusion is well-known as a safe and effective procedure in HD patients.8–12) However, the optimal choice between PTA and stent placement in the management of central venous stenosis and occlusion still remains controversial. Some groups routinely perform stent placement for central venous stenosis; they have reported improved patency rates compared to those with PTA alone.8,9) On the contrary, other groups reported that the primary patencies between angioplasty and stent were not significantly different.10,11) Further, Ozyer et al.12) reported that stent placement for central venous stenosis or occlusion led to a significantly lower primary patency rate than PTA but added to the longevity of vein patency in angioplasty-resistant lesions; therefore, stent placement should be considered in such angioplasty-resistant lesions. The most commonly used stents for central venous stenosis or occlusion are self-expandable stents. On the other hand, balloon-expandable stents are used only when the stenosis is short12) and the diameter is large.13)

The pull-through technique has been reported in the treatment of totally occluded iliac arteries14) or the high-grade stenosis of central veins.15) The technique provides sufficient traction to deliver a large-sized catheter device even when there are sharply angled lesions, as in the present patient.

In the present case, because recurrent left subclavian venous stenosis after repeat PTA developed in an HD patient, stent placement was chosen. Although there has been the disadvantage that a balloon-expandable stent may have developed compression or deformation after deployment,13) we decided to use a Palmaz stent instead of a self-expandable stent because the subclavian vein was larger than the self-expandable stent available in Japan, with commercial sizes up to 12 mm. Palmaz stent placement was successfully performed for the stenosis employing the pull-through technique, in which a guidewire was passed from the left internal jugular vein to the access vein. There has been one report of a stent being placed for central venous occlusion or stenosis with the use of the pull-through technique between the femoral vein and access vein.11) To our knowledge, however, there has been no report of stent placement employing the pull-through technique from the left internal jugular vein to the access vein for subclavian venous stenosis in an HD patient with a PLSVC. If we had used the pull-through technique between the femoral vein and access vein in this case, severe complications such as arrhythmia and cardiac arrest would have developed because the guidewire would have passed through the coronary sinus.

In conclusion, we should be aware of the existence of a PLSVC, which is not exceedingly rare, although uncommon, in interventional procedures such as catheterization from the left jugular vein or the left subclavian vein and PTA for left subclavian venous stenosis. Although it is rare to perform endovascular stent placement for a left subclavian venous stenosis or occlusion in patients with a PLSVC, the pull-through technique between the left internal jugular vein and access vein may be safe and effective.

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**Case Report**

# Patient with a Massive Idiopathic Thrombosis in the Inferior Vena Cava

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**A 50 year-old man with no significant medical history was admitted for dyspnea and left femoral swelling. Contrast-enhanced computed tomography revealed pulmonary thromboembolism (PTE) and a thrombus in the inferior vena cava (IVC). The thrombus extended from the proximal IVC to the left popliteal vein. Therefore, we decided that an IVC filter insertion was difficult to indicate. Urgent IVC and peripheral vein thrombectomy was performed under cardiopulmonary bypass. On postoperative day 1, venous ultrasonography showed residual deep vein thrombosis in the left external iliac–femoral vein and the popliteal vein. The IVC filter insertion was performed to prevent the recurrence of PTE.**

***Keywords:*** ivc thrombus, ivc filter, deep vein thrombosis

## INTRODUCTION

Deep vein thrombosis (DVT) is a common condition. However, pulmonary thromboembolism (PTE) secondary to DVT is still high mortality. The first-line treatment for DVT is anticoagulation therapy, although, the safety and efficacy of inferior vena cava (IVC) filters are remarkable. IVC filters are commonly used to prevent PTE. However, it is not enough to investigate the indications for the use of IVC filters in DVT patients. Several reports have described IVC thrombus secondary to renal tumor or trauma. Idiopathic IVC thrombosis is very rare, and there is no established treatment procedure for it. In our case, multiplanar reconstruction images revealed a massive IVC thrombus extending from the proximal IVC to the left popliteal vein. Insertion of an IVC filter might have crushed the IVC thrombus and provoked a fatal PTE; therefore, we performed thrombectomy under cardiopulmonary bypass. The length of the excised thrombus was 60 cm. After thrombectomy, venous ultrasonography was performed, and it showed residual floating DVT. The patient had a high risk of recurrent pulmonary embolism. Therefore, we inserted OptEase® filter (Cordis Corporation, USA, NJ), after confirming the removal of the IVC thrombus by using venography. To our knowledge, there are no reports on cases of such a massive IVC thrombus in the literature. The careful examination, for example, contrast-enhanced computed tomography (CT) is essential before IVC filter insertion, whether the patients have complications.

## CASE REPORT

A 50 year-old man with no significant medical history was admitted for dyspnea and left femoral swelling and pain. He took notice on the 2 days before admission. He had a smoking habit (20 cigarettes per day) and was not obese. His vital signs were as follows: blood pressure, 122/86 mmHg; heart rate, 74/minute; and oxygen saturation, 92% (room air). Results of laboratory tests showed that levels of fibrin degradation products (160–320 µg/mL) and D-dimer (8–16 µg/mL) were high. However, levels of protein C, protein S, and anti-phospholipid antibodies were within normal limits. Venous ultrasonography revealed a

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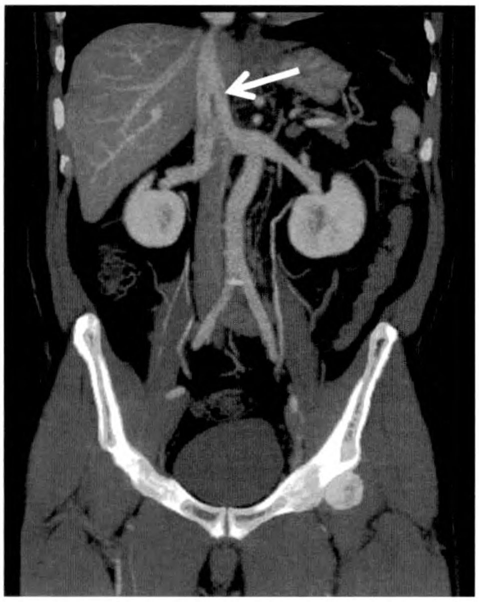

**Fig. 1** Coronal multiplanar volume reformation image showed almost complete occlusion of the inferior vena cava (IVC) distal to the renal vein by the IVC thrombus. The arrow indicates the proximal end of the IVC thrombus.

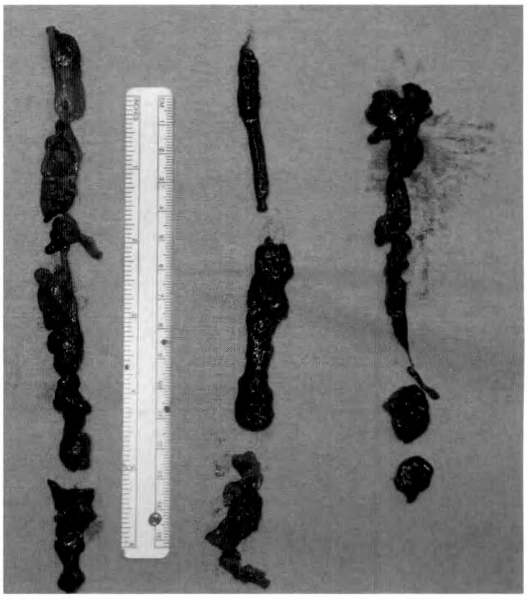

**Fig. 2** Inferior vena cava (IVC) thrombectomy specimen. The left portion is the thrombus from the proximal IVC. The right-most portion was extracted from the left femoral vein.

thrombus extending from the left femoral vein to the popliteal vein and venous occlusion. Contrast-enhanced CT revealed a thrombus in the right pulmonary artery and basal segmental branches. Furthermore, multiplanar reconstruction images revealed an IVC thrombus extending from the proximal part of the IVC and the renal vein junction to the left popliteal vein (**Fig. 1**). Because the insertion of an IVC filter might crush the huge IVC thrombus and provoke a fatal PTE, we decided to immediately perform a thrombectomy by using a Fogarty catheter under cardiopulmonary bypass. Drainage cannulas were inserted superior vena cava and upper IVC via lower right atrium (above hepatic vein). The 7 Fr Fogarty catheter was inserted from the left femoral vein towards the IVC. We also performed peripheral vein thrombectomy. An enormous thrombus (length, approximately 60 cm) was extracted by performing a Fogarty thrombectomy (**Fig. 2**). After the IVC thrombectomy, no thrombus was detected in the right atrium or in venous blood coming from the IVC.

Venous ultrasonography performed on postoperative day 1 showed a residual thrombus extending from the left external iliac vein to the popliteal vein. The possibility of the recurrence of PTE was high; therefore, we inserted the OptEase® filter (Cordis Corporation, USA, NJ). Before inserting the IVC filter, we confirmed the removal of the IVC thrombus by using venography via the right femoral vein. Further, anticoagulation therapy with warfarin was started. CT performed before the patient's discharge from the hospital showed IVC shrinkage and entire removal of the IVC thrombus. However, a residual thrombus extending from the left common iliac vein to the left popliteal vein was detected despite anticoagulation therapy. The patient made satisfactory progress and was discharged on postoperative day 21.

## DISCUSSION AND CONCLUSION

Cases of PTE caused by DVT are sometimes encountered in the emergency room. Hirst et al. reported that the prevalence of PTE was lower in Japanese (0.7%) than in North Americans (15%).[1] Several reports have stated that the proportion of idiopathic venous thromboembolism ranged from 26% to 47%.[2, 3] Our patient showed no complication, malignancy, trauma, or abnormal clotting and had not undergone any prior surgery. IVC thrombosis commonly occurs in patients with renal tumor or trauma. In this case, the thrombus was 60 cm in length. It is the longest IVC ever reported. At first, we intended to insert an IVC filter to prevent the recurrence of PTE because the patient showed no complications and the symptom progressed quickly. Venous ultrasonography could not provide images of the more proximal part of the common iliac vein and IVC. However, enhanced CT images revealed a massive IVC thrombus. The insertion of an IVC filter without detection of a massive IVC thrombus may have resulted in the crushing of the IVC thrombus and development of a lethal PTE. IVC thrombosis with DVT is rare, especially in patients without complications. However, for the patients' safety, a detailed examination by using techniques such as enhanced CT, venous ultrasonography, or venography is required to check the extent of DVT before IVC filter insertion. Usually, venous ultrasonography is most suitable modality to evaluate the extent of DVT. However, venous ultrasonography is difficult to detect the extent of IVC thrombus, because IVC is in the abdominal cavity. Therefore, in this case the enhanced CT is most effective to evaluate DVT including IVC thrombus.

Thrombectomy was performed under cardiopulmonary bypass. There have been cases in which the IVC filter was inserted in the more proximal part of the renal vein. In this case, thrombectomy was performed under cardiopulmonary bypass since IVC filter insertion was difficult to be indicated. Our decision was based on the following reasons:

(1) The multiplanar reconstruction images showed that the thrombus extended to the proximal IVC.

(2) The CT images suggested that this thrombus was unusually massive.

(3) Progression of the thrombus indicated a high possibility of occlusion of the IVC filter.

(4) Thrombectomy under cardiopulmonary bypass could have eliminated the possibility of secondary PTE during the operation.

There is a debate on the indication for IVC filter insertion. Becker et al. reviewed whether the risk associated with filter placement for the prevention of recurrent PTE is justified in cases in which anticoagulation therapy is contraindicated or fails.4) Previous reports have described the following complications of IVC filter insertion: filter migration, insertion-site DVT, erosion or perforation of the filter into the IVC wall, and IVC obstruction and lower extremity venous insufficiency.4) However, Decousus et al. showed that the use of a permanent filter for patients with proximal DVT reduced the occurrence of symptomatic or asymptomatic PTE without major complications. In addition, they also showed that IVC filters had no effect on mortality.5) Therefore, the use of IVC filters increased because IVC filter insertion was easy and reduced complications by technical improvement.6,7) Chung et al. reported that IVC filter insertion was a safe and effective method for preventing PTE.8) Chiou et al. have discussed the use of IVC filters as a prophylactic treatment for proximal free-floating thrombi.9) The incidence of pulmonary embolism has been reported to be 60% in patients who show free-floating parts of an iliofemoral thrombus even after receiving anticoagulation therapy.10) In this case, we inserted an IVC filter on the first day after the thrombectomy because venous ultrasonography showed a mobile residual thrombus in the left external iliac vein. Despite adequate anticoagulant therapy, the CT images taken before the patient's discharge confirmed the presence of DVT extending from the left common iliac vein to the popliteal vein; however, the IVC thrombus was completely removed. We do not recommend the systematic use of IVC filters for all DVT patients. However, in very high-risk patients, an IVC filter must be inserted to prevent lethal PTE. The findings of this case suggest that physicians should carefully evaluate the risks and benefits of inserting an IVC filter in each patient.

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**Case Report**

# Ischemic Colitis Following Transarterial Embolization for Type 2 Endoleak of EVAR: Report of a Case

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**A 71 year old man was diagnosed to have enlargement of abdominal aortic aneurysm due to type 2 endoleak two years after endovascular aneurysm repair (EVAR). 3D-CT demonstrated a type 2 endoleak that originated from the superior mesenteric artery that fed the inferior mesenteric artery and the right iliolumbar artery that flowed into the 4th lumbar artery. Transarterial embolization was performed by means of N-butyl-2-cyanoacrylate (NBCA). After the treatment, he suffered ischemic colitis that extended from the sigmoid colon to the descending colon. Conservative treatment was mainly performed, and clinical improvement was observed over time. He was discharged after 73 postoperative days.**

***Keywords:*** type 2 endoleak, transarterial embolization, ischemic colitis

## INTRODUCTION

Type 2 endoleak is the most common complication following endovascular aortic aneurysm repair (EVAR) in patients with abdominal aortic aneurysm (AAA). Although many type 2 endoleaks resolve spontaneously within a few months, the persistent type is sometimes associated with expansion of the aneurysm sac that leads to rupture; and thereby, requires secondary intervention. This study presents a case of ischemic colitis as a complication following transarterial embolization for type 2 endoleak following EVAR.

## CASE REPORT

A 71 year-old man presented with a 50-mm AAA confirmed by computed tomography (CT). Because of his previous history of multiple laparotomies, including total gastrectomy for gastric cancer, open drainage for acute pancreatic necrosis, and partial colectomy for colon cancer, EVAR with a Zenith® endovascular graft was performed in our university hospital. Although the postoperative course was uneventful, type 2 endoleak was demonstrated in the contrast CT scan at 1 week postoperative. He was discharged and subsequently followed up at our out-patient clinic. The contrast CT scan at 6 months after the procedure showed that type 2 endoleak persisted. However, the size of the aneurysm sac did not change; hence, we opted for watchful waiting of the endoleak. Two years after the procedure, the periodic contrast CT scan revealed expansion of the aneurysm sac at 11 mm with persistent type 2 endoleak (**Fig. 1A**). The 3D-CT also demonstrated that the type 2 endoleak originated from two channels; first from the superior mesenteric artery that fed the inferior mesenteric artery (IMA) (**Fig. 1B**) and the other one from the right iliolumbar artery that flowed into the 4th lumbar artery (**Fig. 1C**). The expansion of the aneurysm sac was caused by the type 2 endoleak. He was admitted to undergo transarterial

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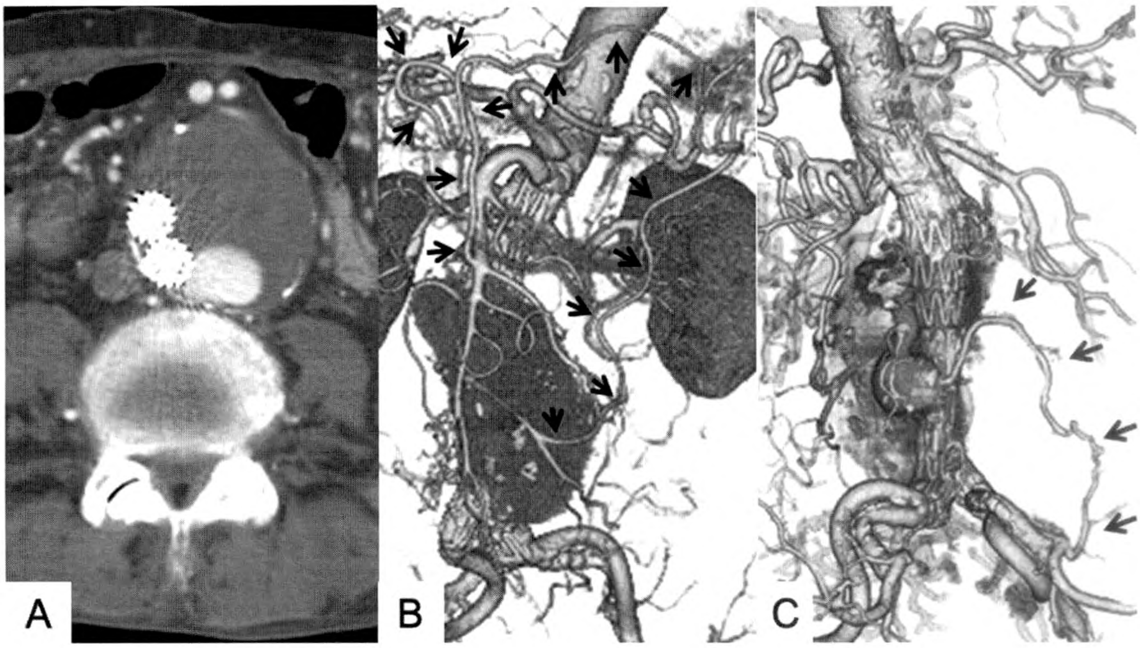

**Fig. 1** Contrast CT scan at two years after EVAR: 11-mm expansion of the aneurysm sac with the persistent type 2 endoleak (**A**). 3D-CT of type 2 endoleak originating from two channels; first, from the superior mesenteric artery that fed the IMA (**B**) and the other, from the right iliolumbar artery that flowed into the 4th lumbar artery (**C**).

embolization for type 2 endoleak.

Angiography was performed via the left femoral artery. Right hypogastric angiography demonstrated enhancement of the aneurysm sac from the iliolumbar artery (**Fig. 2A**). Since the blood flow to the aneurysm sac from the right iliolumbar artery was predominant, insertion of a 2 Fr. microcatheter was tried to follow the path of this collateral into the aneurysm sac in order to perform coil embolization of the endoleak cavity but was not successful. Therefore, 0.3 mL of N-butyl-2-cyanoacrylate (NBCA) was injected with 1.2 mL of ethyl ester of iodinated poppy-seed oil fatty acid at the ostium of the right iliolumbar artery, in which fluoroscopy revealed filling of the endoleak cavity from the iliolumbar artery (**Fig. 2B**). Postoperative enhanced CT demonstrated the disappearance of the endoleak.

During the postoperative period, he complained of abdominal pain and diarrhea. Ileus and bloody stool were noted on the fifth postoperative day. Endoscopy demonstrated severe edema and inflammation of the mucosa, which extended from the sigmoid colon to the descending colon, with contact bleeding and ulceration (**Fig. 3**). Because endoscopy confirmed ischemic colitis, he was placed on bowel rest and intravenous fluid supply was started. On the 34th postoperative day, endoscopy demonstrated healed ulceration but stenosis on the descending colon, which was the previous site of partial colectomy for colon cancer. He underwent endoscopic bougie dilatation of the stenotic descending colon. Clinical improvement was observed over time and he was discharged after 73 postoperative days.

## DISCUSSION

Type 2 endoleak is the most common complication encountered following EVAR. It occurs in about 20% of patients after EVAR. A persistent type 2 endoleak is associated with an increased incidence of adverse outcomes, including aneurysm sac growth, need for reintervention or conversion to open repair, and rupture.[1] Type 2 endoleak occurs when there is retrograde blood flow into the aneurysm sac via excluded aortic branches, most commonly the IMA or a lumbar artery. In this case, two channels were identified on preoperative 3D-CT; one from the superior mesenteric artery that fed the IMA and another from the right iliolumbar artery that flowed into the 4th lumbar artery. It was unclear which channel supplied the blood flow into the endoleak cavity. However, contrast flowed into the IMA via the aneurysm sac by hypogastric angiography, which demonstrated both channels served as collaterals that supply blood to the IMA. Therefore, it was considered that embolization of

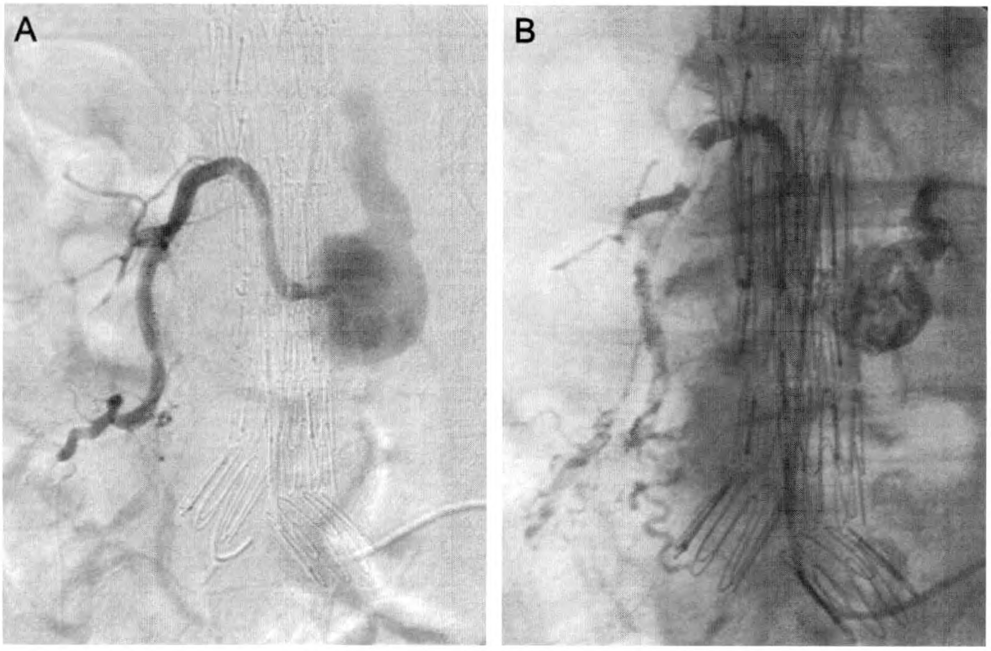

**Fig. 2** Right hypogastric angiography of the enhancement of the aneurysm sac from the iliolumbar artery (**A**). Fluoroscopy of the full spreading of NBCA administered with ethyl ester of iodinated poppy-seed oil fatty acid through the iliolumbar artery into the endoleak cavity (**B**).

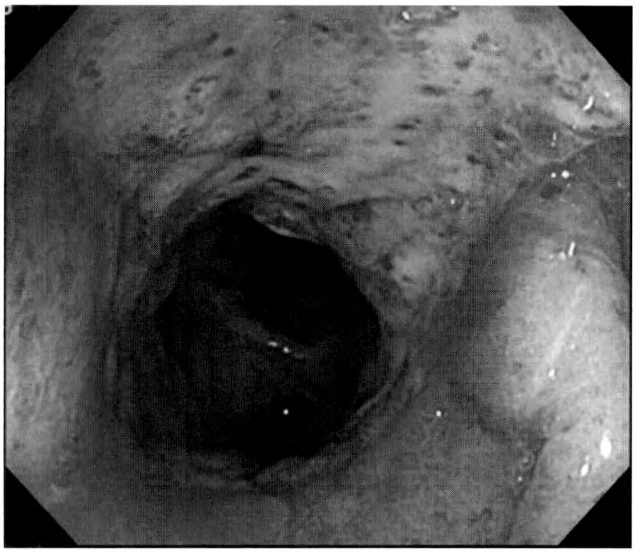

**Fig. 3** Endoscopy of severe inflammation of the mucosa, extending from the sigmoid colon to the descending colon, with contact bleeding and ulceration.

the iliolumbar artery contributed to the insufficient blood supply to the IMA and resulted in ischemic colitis.

Several treatments for type 2 endoleak were reported in the previous literature. Although surgical or laparoscopic ligation$^{2)}$ and translumbar embolization$^{3-6)}$ are included, transarterial chemical or coil embolization seems to be the standard option$^{7-10)}$ because the treatment is less invasive. The clinical success rate of transarterial embolization varies. For instance, Baum et al. reported eight patients who underwent successful treatment with transarterial IMA embolization.$^{8)}$ Although no residual endoleaks were detected on the 30-day postembolization CT scan, seven (87.5%) of these eight patients had recurrent type 2 endoleak.$^{4)}$ On the other hand, Haulon et al. presented 18 patients who underwent transarterial embolization with type 2 endoleak; wherein, the aneurysm sac shrank in 13 (72.2%) of 18 during follow-up periods and a new type 2 endoleak was diagnosed in only two (11.1%) patients.$^{10)}$ The difference between these two clinical success rates of transarterial embolization depends on target vessels. Therefore, in Haulon's study, the injection of biologic glue led to embolization of the endoleak cavity, which connected the feeding vessels and drainage vessels. Meanwhile, coil embolization of the IMA in Baum's study targeted only one of the feeding vessels. These results indicate that single vessel arterial embolization is ineffective because type 2 endoleak is a dynamic structure that resembles an arteriovenous malformation being fed by multiple vessels and the embolized vessels can be replaced by another one. In order to succeed the treatment, embolization of the endoleak cavity in addition to the feeding artery is effective.$^{11)}$

Biologic glue can easily occlude not only the feeding vessels but also the endoleak cavity itself. Liquid embolic agents similar to biologic glue are also available especially in case a microcatheter cannot pass through the collateral into the endoleak cavity. The intraoperative fluoroscopy showed that NBCA instilled from the ostium of the iliolumbar artery selectively filled the endoleak cavity in this case. NBCA 0.3 mL mixed with 1.2 mL of ethyl ester of iodinated poppy-seed oil fatty acid (1:4 concentration) was prepared. NBCA can easily control the coagulation time by adjustment of mixture ratio with ethyl ester of iodinated poppy-seed oil fatty acid. However, the injection of liquid embolic agent could lead to microembolization in the periphery of IMA and/or in the collaterals supplying blood flow to the colon. Bush et al. reported colonic necrosis subsequent to transarterial thrombin embolization for type 2 endoleak.12) On the other hand, Gambaro et al. presented ischemic colitis following translumbar thrombin injection for treatment of type 2 endoleak.13) These literatures indicate that neither transarterial nor translumbar injection of liquid embolic agent for the treatment of type 2 endoleak can avoid the risk of ischemic colitis from microembolization. When the microcatheter could not go through the collateral from the iliolumbar artery into the aneurysm sac in this case, NBCA injection was then performed at the ostium of iliolumbar artery. However, considering the risk of microembolization into the IMA following the large volume of NBCA injection from the ostium of iliolumbar artery, coil embolization of the endoleak cavity through another channel connecting the superior mesenteric artery and IMA should have been performed. Although translumbar coil embolization of the endoleak cavity is an alternative treatment for type 2 endoleak in case transarterial embolization cannot succeed, it is still challenging. It is true that NBCA for embolization is convenient and cost-effective, but its use requires careful titration in order to prevent complications.

## CONCLUSIONS

In conclusion, this study presents a case of ischemic colitis as a complication following transarterial embolization for a type 2 endoleak of EVAR. Type 2 endoleak sometimes play an important role in supplying blood to the visceral organs and the treatment for type 2 endoleak potentially has a risk of organ ischemia.

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**Case Report**

# Late-Onset Primary Intestinal Lymphangiectasia Successfully Managed with Octreotide: A Case Report

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**We report a case of a patient with late-onset primary lymphangiectasia whose persistent diarrhoea was successfully managed with octreotide. A 63 year-old man visited our clinic with a complaint of worsening general edema. Gastrointestinal endoscopy revealed typical whitish jejunal villi, which suggested primary intestinal lymphangiectasia. Despite a diet, supplemented with medium-chain triglycerides; antiplasmin therapy; oral corticosteroids; and surgery, including pericardial window and lymphaticovenous anastomoses; his symptoms, including watery diarrhoea, showed no improvement. After administration of octreotide, his persistent diarrhoea resolved within a couple of days. Octreotide was continued for 2 months. Thereafter, his diarrhoea has not recurred for 6 months.**

***Keywords:*** intestinal lymphangiectasia, octreotide, protein-losing enteropathy

## INTRODUCTION

Primary intestinal lymphangiectasia (PIL), first described by Waldmann et al. in 1961,[1] is a rare disorder characterized by dilated intestinal lacteals that cause leakage of the lymph into the small bowel lumen, which results in protein-losing enteropathy (PLE).[2] Most patients are diagnosed with PIL in childhood. Clinical presentation of the disease includes general edema, diarrhea, and symptoms associated with PLE and malabsorption syndrome. We report a case of a patient who presented with PIL for the first time at the age of 60 years, and persistent diarrhea of the patient was dramatically improved with octreotide.

## CASE REPORT

A 63 year old man was referred to our clinic because of progressive, general edema and a recent increase in body weight by 5 kg. He reported swelling that he had noticed for the first time in the upper extremities, in the face within 3 years from the onset, and subsequently in the lower extremities. Physical examination revealed pitting edema of the arms and legs, as well as of the face. No remarkable edema was seen in the body trunk during his first visit. Consultations with physicians did not indicate particular problems in the cardiac, renal, and hepatic function and neither in thyroid function. He had surgery for bilateral hydrocele testis at 40 years of age; otherwise, his medical and family histories were unremarkable.

Laboratory tests revealed the following values (normal values in parentheses): serum total protein, 5.3 g/dL (6.8–8.3 g/dL) and albumin, 3.0 mg/dL (3.7–4.7 mg/dL). Immunoglobulin G (IgG) concentration, 741.0 mg/dL (870–1700 mg/dL), depleted while maintaining IgA 151.0 mg/dL (110–410 mg/dL) and IgM 39.9 mg/dL (33–190 mg/dL) in the normal range. Lymphocytopenia 22.7% (30.0–46.0%) and hypocalcemia 2.20 mmol/L (2.30–2.65 mmol/L) were also observed. Lymphangioscintigraphy (LAS) in the extremities showed the absence of lymph trunks and inguinal and axillary nodes, with

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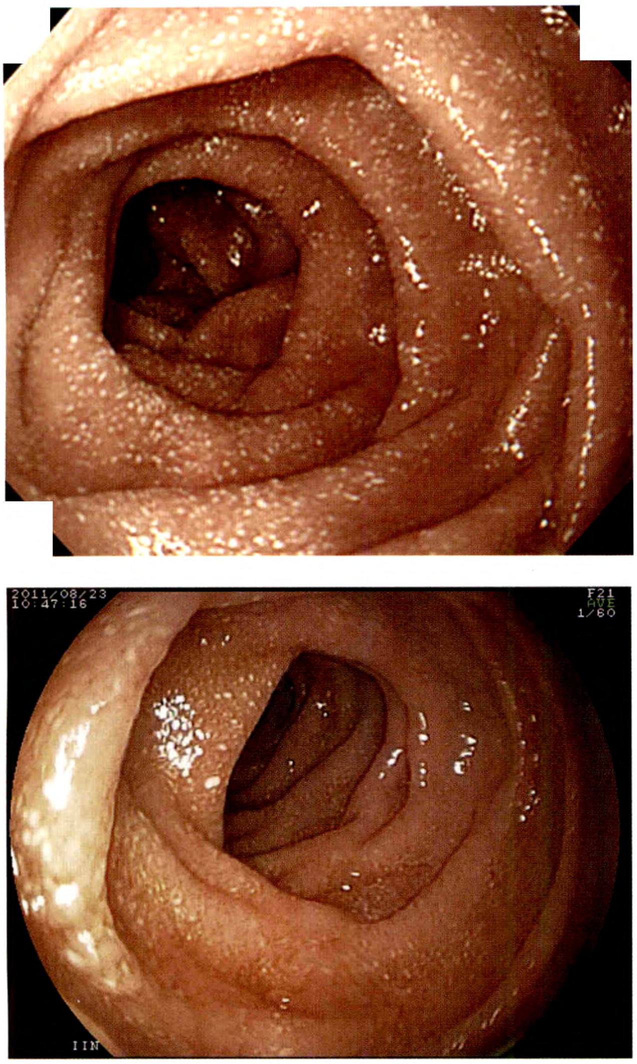

**Fig. 1** Gastrointestinal endoscopy (Duodenum). Before treatment with octreotide, tiny scattered white spots, ie, whitish jejunal villi, indicating dilated lymphatics filled with fat droplets were seen on the entire duodenal wall. (**A**) Whitish jejunal villi markedly reduced even 6 months after discontinuation of octreotide. (**B**)

significant accumulation of contrast medium in distal extremities. Since his skin condition was preserved, it seemed that he had a complication of grade I primary lymphedema in the upper and the lower extremities.

Chest radiograph, computed tomography (CT) scan, and echocardiography showed pericardial and bilateral pleural effusion but few ascites. Magnetic resonance lymphography showed a patent thoracic duct and no dilatation of the cisterna chyli. No remarkable dilatation was found in the intraabdominal and retroperitoneal lymphatics. Gastrointestinal endoscopy and capsule endoscopy revealed typical whitish jejunal villi and intestinal edema (**Fig. 1A**). $^{99m}$Tc-labeled human serum albumin ($^{99m}$Tc–HAS) scintigraphy showed patchy leak of albumin in the duodenum and the entire small intestine (**Fig. 2**). Biopsies from the duodenal wall did not show a typical picture of dilated lymphatics in the lamina propria,[3] but instead showed mildly dilated lymphatics in the deeper layer. Since no other underlying diseases, including inflammatory bowel disease, infection, celiac disease, etc., were found in the gastrointestinal system of the patient, his condition was diagnosed as PLE due to PIL associated with primary lymphedema in the extremities.

A low-fat diet with supplementary medium-chain triglycerides (MCT), diuretics, and complex physical therapy for lymphedema were immediately initiated at the outpatient clinic. Although the serum albumin level had been maintained around 3.0 g/dL or higher, the patient had iron-deficiency anemia and worsening lymphocytopenia and hypocalcemia. At around 6 months from his first visit, he complained of watery diarrhea 5 to 8 times/day, as well as increasing shortness of breath, which was caused by increasing pleural and pericardial effusion. His symptoms did not improve despite an increase in doses of diuretics and antiplasmin therapy (tranexamic acid 1 g, 3 times/day) followed by the administration of oral corticosteroids (prednisolone, 5 mg/day).

After a year of treatment at the outpatient clinic with no improvement in his condition, the patient was eventually admitted and kept on complete, total parenteral nutrition (TPN). Following cessation of oral intake, his watery diarrhea had stopped. We performed the video-assisted, thoracoscopic pericardial window procedure, for the reduction of right atrial pressure and microsurgical lymphaticovenous anastomoses in both groins, and we had expected that these procedures would have favorable effects on overall lymphatic drainage. Both pleural and pericardial effusions were serous and not chylous in nature. The inguinal lymphatics were dilated and filled with clear lymph, but not chyle. On postoperative day 5, namely after 12 days of TPN, light meal was re-started and then watery diarrhea recurred immediately. Finally, on post-operative day 8, administration of 100 μg of subcutaneous octreotide twice daily was initiated. From the next day, his diarrhea gradually disappeared, and eventually, he had normal bowel movements over a couple of days. Subsequently, octreotide was administered as a slow-release formulation (Sandostatin LAR® 20 mg), and he was discharged on postoperative day 17. Slow-release octreotide was injected once every 4 weeks at the outpatient clinic. After 3 injections, however, the patient was

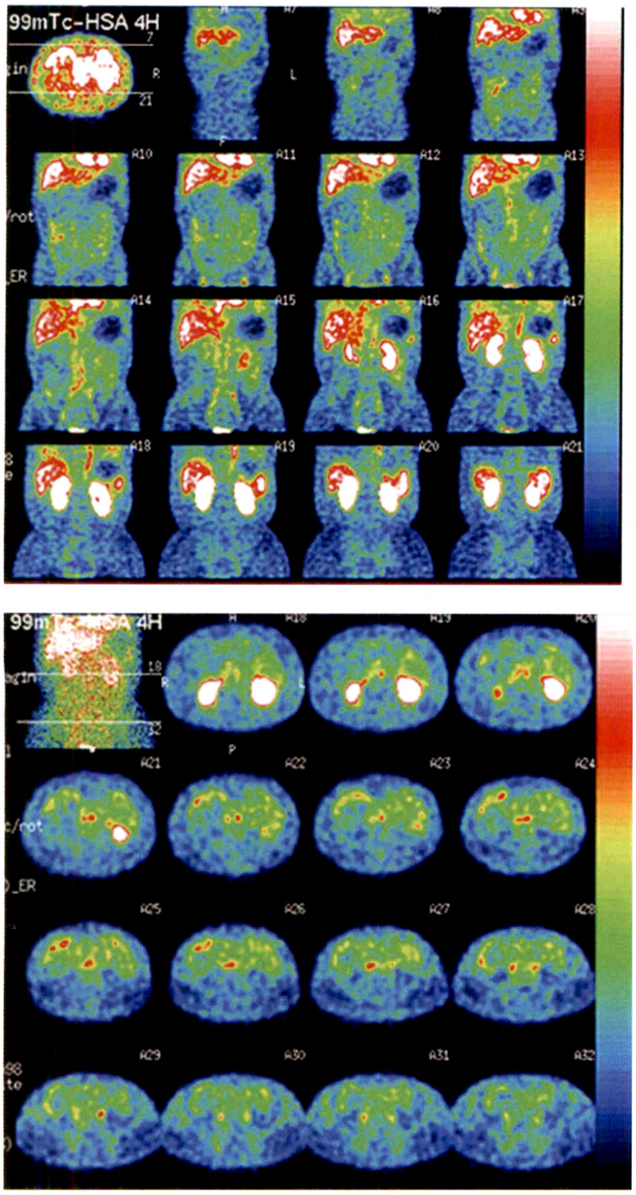

**Fig. 2** $^{99m}$Tc-labeled human serum albumin scintigraphy. Multiple and patchy leakage of albumin (seen as red spots) is scattered in the entire length of the duodenum and the small intestine.

unable to afford it, and the injection was discontinued.

At 8 months from discharge, 6 months after the discontinuation of slow-release octreotide, the patient has not experienced watery diarrhea, and recent gastrointestinal endoscopy showed reduced whitish jejunal villi in the duodenum (**Fig. 1B**), but mild hypoalbuminemia (3.3 g/dL) causing edema continues to persist.

## DISCUSSION

Since PIL can be asymptomatic, the exact prevalence of this disease, as well as its cause and pathogenesis, remain to be clarified.[2,4] PIL is usually diagnosed before 3 years of age, but may be diagnosed in adults. However, late presentation such as 60 years of age or older, similar to that in our patient, is very rare. Primary lymphedema in the extremities can be associated with PIL as in the case of our patient. The diarrhea in this patient started 6 months after his first visit. At the time of the first gastrointestinal endoscopy, however, intestinal edema had already been observed. Therefore, we speculate that inflammation and edema progressed and eventually, they caused watery diarrhea, which further worsened these symptoms.

Currently, treatment options for PIL are limited, and a definite treatment option remains to be established.[2] Diet supplemented with MCT is an essential component and should be continued throughout the life of the patient. Although antiplasmin therapy using tranexamic acid is effective in some patients, it was not effective in our patient. Higher doses of corticosteroids may be prescribed for PLE with underlying inflammatory or autoimmune diseases, but the efficacy of corticosteroids for PIL is uncertain. Since PIL can develop into uncontrollable intestinal bleeding or ileus which may require emergent small bowel resection in the later course of the disease,[5] treatment with high-dose steroid was reserved as a last resort in our patient. Although small bowel resection may be effective, it is indicated only in cases of patients with localized PIL, and thus, it was not performed in our patient. Indication of lymphaticovenous anastomoses for this patient may be controversial. Although it was not described, there was one episode of cellulitis before admission, possibly due to lymphatic congestion. He had not experienced cellulitis since surgery; however, this might have been the result of an overall improvement in lymphatic drainage by the reduction of right atrial pressure in the pericardial window procedure.

Octreotide, a somatostatin analogue, has been shown to alleviate various types of diarrhea. Although little is known about the mechanism of action of somatostatin, particularly in the treatment of PIL, inhibition of gastrointestinal vasoactive peptides, stimulation of the autonomic nervous system,[6] and reduction in intestinal absorption of fats are the proposed mechanisms of action.[7,8] Sari et al. studied the long-term safety of octreotide in 6 patients for up to 37 months.[9] One patient had pancreatitis, but no other adverse effects were observed in the other patients.

The cost of continuing octreotide, which is not covered by insurance, is a serious problem in our country. Since hypoalbuminemia and general edema in our patient did not show sufficient improvement, we proposed to increase the doses of octreotide. However, the patient declined treatment for financial reasons. Sandostatin LAR® 20 mg costs \ 237000, which is certainly not affordable for ordinary people every 4 weeks. Our results show that octreotide can exhibit favorable effects for up to 6 months along with pathological improvement. Kuroiwa et al. reported that discontinuing octreotide resulted in recurrence of symptoms, which could be improved by re-starting octreotide.(10) Therefore, although the regular administration is desirable, the short-term use of octreotide may be considered depending on the symptoms.

## CONCLUSION

We reported the case of a patient with PIL causing PLE successfully treated with octreotide. Although it is not curative, octreotide seemed particularly useful in controlling diarrhea in our patient.

## ACKNOWLEDGEMENTS

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**Case Report**

# Hepatic Artery Pseudoaneurysm with Extrahepatic Biliary Obstruction

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**Hepatic artery pseudoaneurysms are a rare complication of chronic pancreatitis. However, giant pseudoaneurysms (80 mm) and complicated biliary obstructions are extremely rare. This article reports a 75 year-old man with chronic pancreatitis that presented as upper abdominal pain and obstructive jaundice. Computed tomography revealed a hepatic artery pseudoaneurysm measuring 80 × 72 × 70 mm. We performed aneurysm resection and common hepatic artery bypass, using a great saphenous vein graft in the patient. The postoperative course was uneventful, and he was discharged on the 10th postoperative day. However, on the 135th postoperative day, he died of massive hemorrhage into the peritoneal cavity.**

***Keywords:*** visceral artery, hepatic artery, pseudoaneurysm

## INTRODUCTION

Visceral artery aneurysms are rare but potentially life-threatening. Pseudoaneurysms that occur as a consequence of chronic pancreatitis are associated with significant morbidity and mortality because of potential bleeding. Major hemorrhage is a rare but lethal complication of pancreatitis. Rupture may present as either fatal bleeding into a pseudocyst, the peritoneal cavity, or the retroperitoneum, or erosion into the stomach, pancreatic duct, or bile ducts.[1,2] Pseudoaneurysm in conjunction with chronic pancreatitis often occurs in association with the splenic artery. Hepatic artery aneurysms are comparatively rare. Traditional therapy has been surgical resection or ligation or endovascular embolization. These treatment options depend on the presentation of the patient and location of the aneurysm.[3] We herein describe a case of a giant pseudoaneurysm of the common hepatic artery in a patient who presented with abdominal pain and extrahepatic biliary obstruction without bleeding.

## CASE REPORT

The patient was a 75 year-old man who was an alcoholic and former smoker. He had a 2 year history of longstanding epigastric pain. Chronic pancreatitis had been previously detected and was controlled. There was no history of open surgery. Abdominal examination results showed a pulsating palpable mass, and blood examination results revealed significantly elevated serum total bilirubin (1.89 mg/dl), serum direct bilirubin (1.27 mg/dl), aspartate aminotransferase (305 mU/ml), alanine aminotransferase (207 mU/ml), alkaline phosphatase (693 mU/ml), and gamma-guanosine triphosphate (291 mU/ml). He was subsequently diagnosed with arterial aneurysm and obstructive jaundice without symptoms of icterus. The patient was admitted to our center and underwent further evaluation.

The patient was initially evaluated elsewhere with abdominal ultrasonography, which revealed distention of the intrahepatic bile duct, stenosis of the lower part of the common bile duct, and an aneurysm (80 × 72 × 70 mm) contiguous with the celiac artery. We performed computed tomography (CT) with intravenous contrast to assess the nature of the mass. The scan revealed a heterogeneous 80 × 72 × 70-mm mass involving the

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head of the pancreas (**Fig. 1a**) and features of chronic pancreatitis with multiple foci of calcifications in the pancreatic duct and parenchyma involving the body and tail. The pancreatic duct was dilated. However, the *stage of chronic pancreatitis was not clear,* the inflammation of the pancreas had not been active, and exacerbation of the pancreatitis was not detected in CT. Three-dimensional CT (3D-CT) revealed that the aneurysm arose from the origin of the common hepatic artery (**Fig. 1b**). Selective arteriography of the celiac trunk revealed the irregular lumen of the common hepatic artery filled with an intramural thrombus (**Fig. 1c**). The proper hepatic artery and right gastric artery arose from the pseudoaneurysm. The bifurcation of the gastroduodenal artery was not clearly detected on preoperative angiography or CT. The pseudoaneurysm was caused by rupture of the common hepatic arterial wall. Any other aneurysm was not detected on the preoperative examinations. Because there were no signs of rupture or bleeding, the patient was a candidate for elective treatment. The patient fasted and did not undergo preoperative reduction for cholestasis. The blood chemistry values were moderately improved. In addition to the large size of the pseudoaneurysm, which placed it at risk for rupture, and the difficult location for arterial embolization, the patient had no risk factors for surgery. Therefore, it was determined that he would be treated surgically.

The operation was performed through an upper median laparotomy. The pseudoaneurysm was densely adhered to the stomach and retroperitoneum. The lesser sac was entered by dividing the gastrocolic omentum. The stomach was separated from the pseudoaneurysm and pancreas by careful dissection (**Fig. 2**). Proximal vascular control of the common hepatic artery was achieved near its origin. Because the outflow artery from the aneurysm was densely adhered to the aneurysmal wall, we closed the outflow (right gastric artery and proper hepatic artery) from the inside of the aneurysm. The inflow and outflow vessels were ligated, and the aneurysm was resected. A distal and proximal common hepatic artery bypass using a great saphenous vein graft was then performed.

The postoperative period was uneventful, and follow-up CT on the 8th postoperative day revealed successful anastomosis of the common hepatic artery and vein graft (**Fig. 3**). The blood chemistry values were promptly improved to normal levels. The patient was discharged on the 10th postoperative day. He visited the hospital for treatment once during several months without complications. However, on the 135th postoperative day, he was

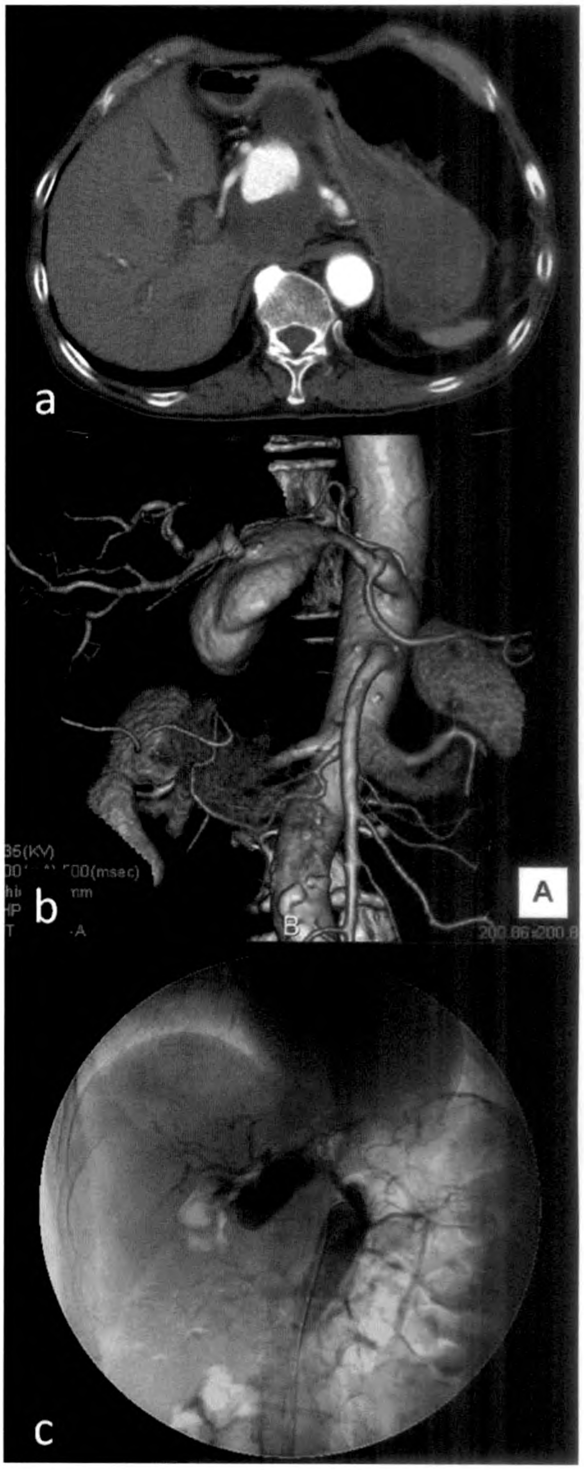

**Fig. 1** (**a**) Abdominal contrast-enhanced computed tomography showed a pseudoaneurysm measuring 80 × 72 mm on the ventral side of the pancreatic head. (**b**) Three-dimensional computed tomography showed that the aneurysm arose from a branch of the common hepatic artery. (**c**) A celiac axis angiogram confirmed that the pseudoaneurysm arose from the common hepatic artery and showed that the irregular lumen of the common hepatic artery was filled with the intramural thrombus.

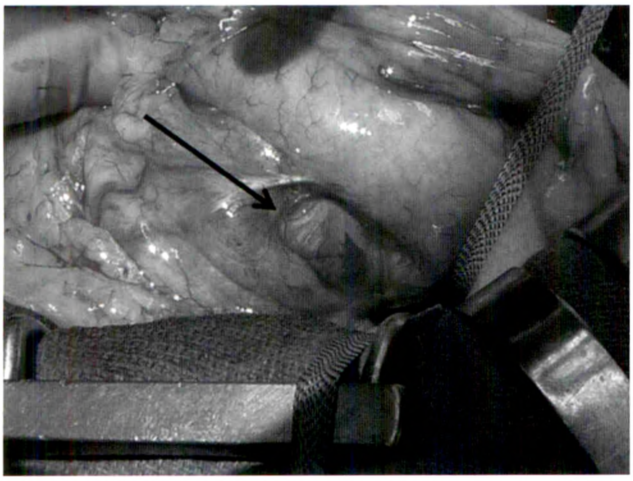

**Fig. 2** Intraoperative photograph showed the hepatic artery pseudoaneurysm. Solid arrow indicates the pseudoaneurysm.

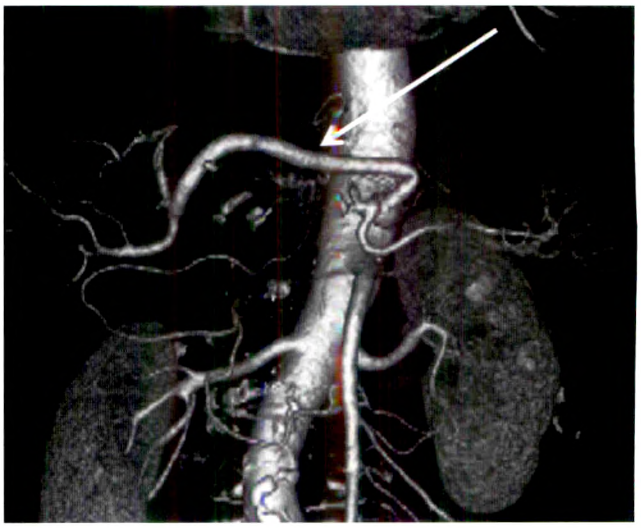

**Fig. 3** Follow-up 3-dimensional computed tomography showed successful anastomosis. Solid arrow indicates the saphenous vein graft.

transported to our center with cardiopulmonary arrest and was confirmed dead. From the autopsy, the cause of death was assumed to be massive hemorrhage into the peritoneal cavity from the artery around the head of the pancreas. Any other aneurysm was not newly detected. There were no problems associated with the common hepatic artery bypass site.

## DISCUSSION

Visceral artery pseudoaneurysms are uncommon. They usually develop secondary to pancreatic disease, with incidence ranging between 10% and 17% in patients with chronic pancreatitis. They have been reported as a late complication, occurring an average of 2 to 3 years after the first episode of pancreatitis, after repeated acute bouts in patients with chronic pancreatitis.[4,5] The splenic artery is the most commonly involved vessel, accounting for half of cases of pseudoaneurysms in chronic pancreatitis, particularly because of its anatomic location.[6] The frequency of hepatic artery pseudoaneurysms due to chronic pancreatitis is comparatively uncommon at 2% to 12%.[2,7] However, since the 1980s, the growing use of percutaneous diagnostic and endoscope therapeutic procedures on the biliary tract has resulted in an increased number of visceral artery pseudoaneurysms, especially of the hepatic artery.[7]

Rupture of a pseudoaneurysm in the gastrointestinal tract is a life-threatening event that is associated with a mortality rate of approximately 75% to 90%.[2,6] The pathogenesis of hepatic artery pseudoaneurysms is not well understood. Pancreatitis, abdominal trauma, and iatrogenic causes (e.g., prior abdominal surgery or endovascular interventions) have been reported as risk factors for hepatic artery pseudoaneurysm.[1,3,6,8] In the present case, chronic pancreatitis seemed to play a role in weakening the common hepatic artery wall. The mechanisms of pseudoaneurysm formation in pancreatitis include inflammation with enzymatic digestion of the pancreatic or peripancreatic artery, visceral artery erosion by pseudocysts, and pseudocyst erosion into the bowel wall and intramural artery.[9]

Most pseudoaneurysms commonly present with abdominal pain or gastrointestinal hemorrhage or as a pulsatile abdominal mass accompanied by bruit.[3,8] As in this case, obstructive jaundice is an extremely rare clinical symptom of hepatic artery pseudoaneurysm.

Diagnosis is usually made from CT or transcatheter angiography results. Moreover, 3D-CT has been performed recently and is reportedly very useful for diagnosis, showing images of optimal directions and being less invasive.[10] In the present case, the location of pseudoaneurysm was easily diagnosed by 3D-CT. It revealed that the pseudoaneurysm arose from the common hepatic artery, and this was confirmed at surgery.

If a hepatic artery pseudoaneurysm ruptures, the patient faces a severely life-threatening condition that requires emergency treatment. However, because of its rarity, no strong consensus exists on the indications for treating visceral artery aneurysm. Marone et al. reported that >2-cm aneurysms with a rapid growth rate and symptoms attributable to aneurysm seem to be associated with conditions imposing aggressive treatment.[7) The traditional therapy for visceral artery aneurysms has been surgical resection or ligation of the aneurysm. Recently, endovascular treatment (coil embolization and stent grafting) has been an alternative to open surgical repair and has become increasingly popular.[4) Because of the development of imaging techniques and percutaneous procedures, there are many reports of successful endovascular treatment and low morbidity and mortality.[1,2,6–8) On the other hand, there is a large study describing the management of hepatic artery aneurysm. It showed that endovascular treatment carries mortality and success rates similar to those of operative strategies.[7) The most frequent complication is the persistent blood flow in the pseudoaneurysm, which is usually caused by a proximal occlusion without distal closure of the artery, resulting in retrograde filling of the pseudoaneurysm through collateral vessels.[6) It is difficult to completely pack a large saccular pseudoaneurysm with coils, leading to persistent expansion of the residual sac. Although an endovascular approach could represent a valid alternative for high-risk patients, surgical treatment remains the standard.[7) Open surgery was the preferred approach in our case because of difficulty in embolization of the cavity, in addition to the need for surgical release of the common bile duct obstruction, by the pseudoaneurysm. However, occlusion of the common hepatic artery has no clinical consequences in the presence of a normally patent portal vein. Aneurysmectomy and bypass grafting were performed in our patient because the portal vein may have been affected by the compression of the aneurysmal wall and adhesion of postoperative inflammation.

In the late stage, one of the most important factors to consider in follow-up of patients is a recurrence of visceral aneurysms. Recurrence of hemorrhage from a pseudoaneurysm secondary to pancreatic inflammation has been reported.[2) In the present case, re-bleeding from arteries around the pancreas seemed to be the cause of death. Rebleeding from known pseudoaneurysms and development of further vascular abnormalities can occur, mandating careful clinical follow-up and repeat angiography as necessary.

## CONCLUSION

Hepatic artery pseudoaneurysms with biliary obstruction are extremely rare. Pseudoaneurysms are unrelated to the severity of pancreatitis, and major hemorrhage can occur irrespective of their size. Therefore, aggressive treatment should be considered once the diagnosis has been made. Endovascular treatment is safe and feasible in selected patients but is not suitable for large aneurysms with several collaterals. Treatment options should be selected based on the presentation of the patient and nature of the aneurysm. Regardless of the activity of the pancreatitis, visceral pseudoaneurysm may develop. We also believe that periodic abdominal imaging (e.g., abdominal ultrasonography or abdominal CT) should be performed to detect recurrence early.

## DISCLOSURE STATEMENT

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Case Report

# Endovascular Surgery for Inflammatory Abdominal Aortic Aneurysm with Contrast Allergy—Usefulness of Carbon Dioxide Angiography and Intravascular Ultrasound: A Case Report

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**We report a patient with inflammatory abdominal aortic aneurysm who underwent endovascular aneurysm repair, despite his having an allergy to iodinated contrast medium and anatomy unsuitable for the procedure. Intravascular ultrasound-guided and $CO_2$-assisted aortic stent graft placement was performed, and the procedures resulted in the successful exclusion of the aneurysm with regression of the mantle sign and resolution of hydronephrosis.**

***Keywords:*** EVAR (endovascular aneurysm repair), inflammatory abdominal aortic aneurysms, contrast allergy

## INTRODUCTION

Inflammatory abdominal aortic aneurysms (IAAAs), which account for 3%–10% of all abdominal aortic aneurysms (AAAs), are characterized by a thick aneurysmal wall with fibrosis and adjacent structure involvement.[1–3] Open surgical treatment of IAAA is inherently accompanied by higher complication and mortality rates because of technical problems related to inflammation and fibrosis.[3] The difficulty of open surgical repair has led to consideration of endovascular aneurysm repair (EVAR) as the first preferred treatment.[4] Recent studies have demonstrated that EVAR resulted in less frequent and less severe intra-operative complications.[5,6] Therefore, the indication for EVAR has been extended to aneurysms unsuitable for open surgery, including IAAAs.

However, EVAR also has some limitations. Anatomical suitability for performing this technique must be carefully examined preoperatively. Intraoperatively, iodinated contrast medium (ICM) is routinely used for evaluating the initial success of the stent graft replacement in spite of its nephrotoxicity. Intravascular ultrasound (IVUS) and $CO_2$ angiography are powerful auxiliary techniques and may be an alternative to ICM for patients who have progressive renal dysfunction or allergies to ICM.

We present a patient with an IAAA who underwent EVAR, despite his having an ICM allergy and anatomy unsuitable for the procedure, and demonstrated the usefulness of IVUS and $CO_2$ angiography.

## CASE REPORT

A 59 year-old male with an infrarenal AAA was admitted to our hospital. Four years previously, he was diagnosed with a small AAA, which enlarged 10 mm in size during these 4 years. The patient complained of slight abdominal pain. Vital signs including blood pressure, pulse rate, and respiratory rate were stable. Laboratory data revealed a C-reactive protein elevation of 2.7 mg/dL. His past history included a severe allergic reaction to ICM, long-term treatment of valvular disease,

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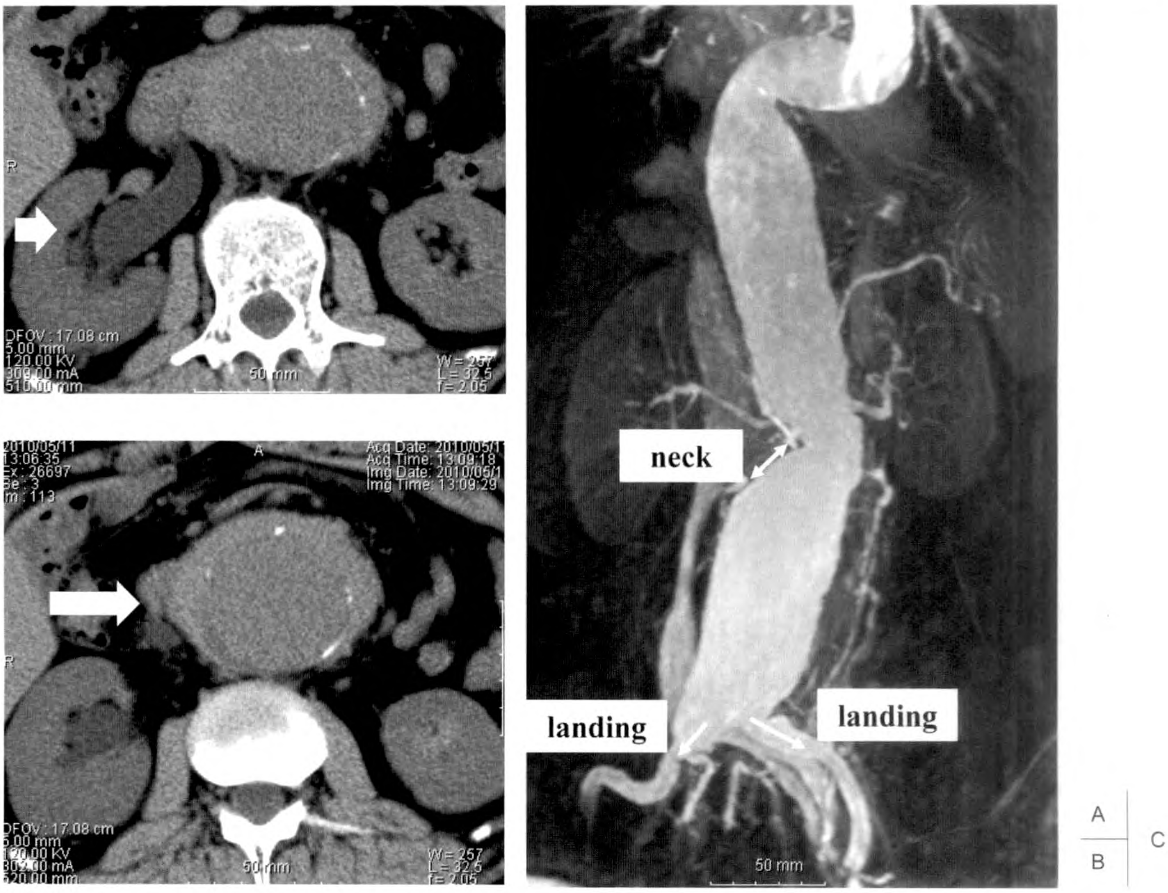

**Fig. 1** Preoperative examination with plain computed tomography (CT) and magnetic resonance imaging (MRI). The CT scan revealed thick periaortic tissues (**A**) and hydronephrosis (white arrow) (**B**). MRI revealed that the shape of aneurysm neck was conical and angulated (**C**).

cerebrovascular infarction, and complex regional pain syndrome after being struck by electric shock. His cardiac function was poor with a left ventricular ejection fraction of 35%, indicating that the patient was unlikely to be a candidate for open aneurysm repair. Plain computed tomography disclosed a thick aortic wall and right hydronephrosis demonstrating a severe inflammatory change in the retroperitoneum (**Fig. 1A** and **1B**). The aneurysm maximal diameters, including thick surrounding tissues, were 64 mm in vertical diameter; and 86 mm, in horizontal diameter. These findings supported the diagnosis of IAAA. We selected endovascular repair, considering the patient's risks and his ardent desire to undergo EVAR after he provided informed consent.

The anatomical suitability of the aneurysm for EVAR was examined. The aneurysm had a conical neck, and the actual landing area was short, approximately 10 mm in length (**Fig. 1C**). We chose the Zenith Flex® endovascular graft (COOK Medical, IN, USA) with a main body diameter of 36 mm. We preferred its suprarenal stent hook for securing the stable fixation in the short proximal neck. In addition, right common iliac artery showed aneurismal change and coil embolization on the hypogastric artery was necessary for preventing type 2 endoleak.

With the patient under general anesthesia, we performed coil embolization on the right hypogastric artery with $CO_2$ angiography (30 cc infusion of $CO_2$) (**Fig. 2A**). Location of the right renal artery, size of devices, and optimal fixation sites were confirmed by high-quality IVUS images (Volcano Visions, PV 8.2F: Volcano Japan Inc., Tokyo, Japan). For the precise placement, we used a sizing-catheter for the measurement and IVUS for the detection of the aortic branch orifices by marking on the monitor with water paint. We could confirm that the stent grafts were accurately placed and deployed just below the renal arteries. Additional bilateral leg deployment was performed under IVUS guidance and $CO_2$ angiography (total $CO_2$, 90 cc).

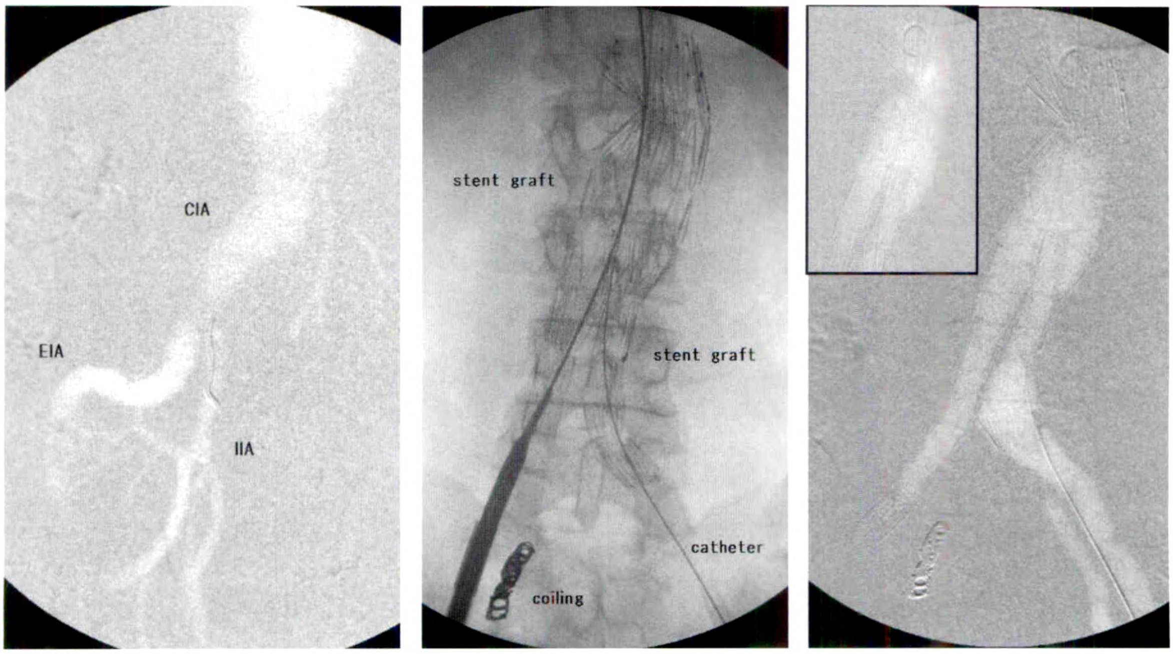

**Fig. 2** Intraoperative X-ray imaging. $CO_2$ angiography provided a sufficiently clear image enough to detect iliac bifurcation for coil embolization (**A**). X-ray imaging revealed the stent graft configuration (**B**). Completion angiography with $CO_2$ angiography revealed no type 1 endoleaks, however, the image was not sufficiently clear to detect the delayed flow of type 2 endoleaks (**C**).
EIA: external iliac artery; IIA: internal iliac artery (hypogastric artery); CIA: common iliac artery

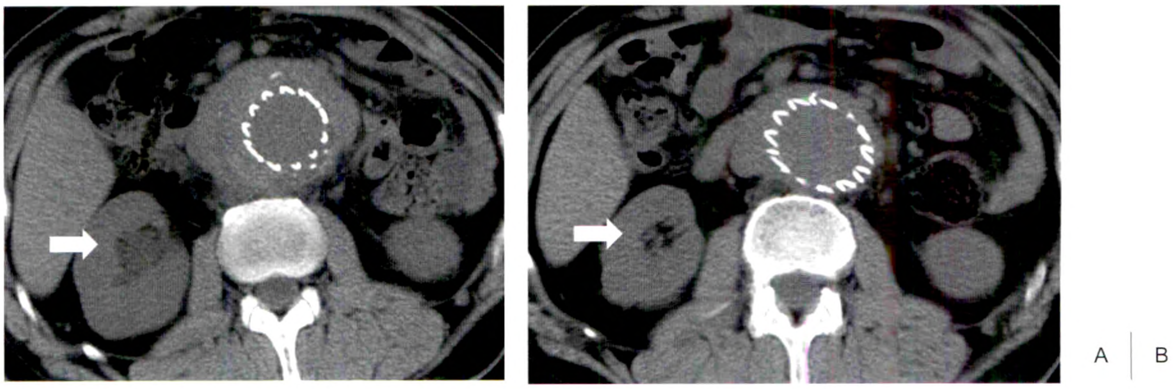

**Fig. 3** Postoperative CT scans (4 days (**A**) and 1 year (**B**) after the operation) revealed the drastic regression of the aneurysm and the improvement of hydronephrosis (white arrows).

The flow within the grafts was good without stenosis (**Fig. 2C**) or delay. No primary endoleak could be visualized by means of the $CO_2$ completion angiography (**Fig. 2C**).

The postoperative course was uneventful. Eighteen months after the procedure, the size of the aneurysm had decreased from 86 mm to 60 mm (**Fig. 3A** and **3B**). In addition, preoperative hydronephrosis resolved with stable renal function (**Fig. 3B**).

## DISCUSSION

IAAA is characterized by inflammatory changes in the periaortic retroperitoneum, featuring a triad of a thickened aneurysm wall, extensive peri-aneurysmal and retroperitoneal fibrosis, and dense adhesions of adjacent abdominal organs.[1–3] Surgical open repair for IAAA occasionally requires skilled procedures and results in worse perioperative mortality than typical AAA surgery. Recently, EVAR has been preferred for IAAA treatment over open surgery because of its excellent initial outcome.[4,7] However, controversial problems have remained such as the lower regression rate of hydronephrosis in Paravastu's review.[8]

Although EVAR has great benefit for high-risk AAA patients, the operative selection requires anatomical suitability. The presented case had 2 disadvantages for EVAR. (1) The aneurysm was anatomically unfit for the use of commercially available stent grafts because it had a short neck (hostile neck) of only 10 mm in length. Aneurysms with a short neck are usually subject to type 1 endoleaks. (2) The patient was allergic to ICM, which meant that ICM could not be used for the intra- and post-EVAR evaluation.

As the proximal type 1 endoleak is associated with a higher risk of late conversion and rupture, it should be treated intraoperatively. We have performed intraoperative management for the proximal site to treat the proximal type 1 endoleak, by applying a noncompliant balloon, an aortic cuff, or a Palmaz$^{TM}$ (Cordis, Miami Lakes, FL, USA) stent, and achieved good results.[9] In this case, the evaluation of the proximal type 1 endoleak might not be sufficient without ICM; thus, we decided to substitute IVUS and $CO_2$ angiography for ICM.

$CO_2$ is reportedly safe and useful, especially for patients with preexisting renal dysfunction, ICM allergy, or hyperthyroidism.[9] Chao et al. revealed that creatinine values remained unchanged in patients who underwent $CO_2$-directed EVAR. Furthermore, the short-term outcomes of patients who underwent $CO_2$-directed EVAR with regard to the incidence of late endoleaks, endograft revision rate, accompanying complications, and the length of hospital stay were equivalent to those of ICM with $CO_2$.[10] From these findings, $CO_2$ as an angiographic contrast agent may be recommended to prevent dialysis and reduce the risk of contrast nephrotoxicity or allergic reactions. However, the chemical features of $CO_2$, namely buoyancy and affinity for water, result in reduced anatomical definition and increased radiation exposure, which account for the disadvantages of the EVAR procedure. The flow of $CO_2$ is slower than that of ICM, which increased the radiation exposure time. In addition, $CO_2$ is absorbed in water too rapidly to evaluate the delayed backflow toward the aneurysmal sac that is typical of type 2 endoleaks.

IVUS has been reportedly adopted as an alternative method to ICM that allows for high-quality imaging for the identification of aortic aneurysm morphology and arterial anatomy, which is helpful in determining graft size and measuring the distance between aortic branches. IVUS can also be used to assess the adequacy of graft apposition after deployment.[11] In our previous study, IVUS successfully reduced the required volume of contrast agents used for angiography during EVAR procedures.[12] Therefore, IVUS helps in reducing the duration and necessity of contrast imaging during endovascular reconstruction and facilitates the precise placement of stent grafts. In our case, the operative time and radiation exposure, both of which are considered disadvantages of $CO_2$ angiography, could be reduced using accurate, immediate, and dynamic images obtained by IVUS. IVUS and $CO_2$ enabled us to visualize the anatomy of the patient adequately. Our experience indicates that the combined use of IVUS and $CO_2$ angiography can provide precise endovascular imaging and reduce the risk of ICM related complications.

Tracking postoperative changes of EVAR with plain CT and transabdominal ultrasound may not be sufficient,[13] especially for evaluating endoleaks. Fortunately, our case demonstrated a drastic regression in aneurysmal diameter, regression of the surrounding tissue of the aorta, and resolution of hydronephrosis, which indicated successful exclusion of the aneurysm.

In conclusion, the combination of $CO_2$ angiography and IVUS for EVAR is a good alternative for patients who are allergic to ICM or those with progressive renal dysfunctions. However, simple $CO_2$ injection is not sufficient to evaluate the delayed flow of type 2 endoleaks. We were fortunately able to demonstrate the successful exclusion of IAAA, which was proven by the improvement of inflammation and regression of the characteristic thick aortic tissue and hydronephrosis.

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**Case Report**

# Endovascular Treatment of Ruptured Intercostal Arteriovenous Fistulas Associated with Neurofibromatosis Type 1

Wakako Fukuda, MD, Satoshi Taniguchi, MD, PhD, and Ikuo Fukuda, MD, PhD

**We report a rare case of ruptured intercostal arteriovenous fistula in a patient with neurofibromatosis type 1. The patient presented with severe back pain. Angiography revealed ruptured intercostal arteriovenous fistulas. Successful coil embolization to occlude the fistulas and the aneurysm resulted in successful recovery of the patient.**

***Keywords:*** neurofibromatosis type 1, intercostal arteriovenous fistula, endovascular treatment

## INTRODUCTION

Neurofibromatosis type 1 (NF1) or von Recklinghausen's disease is an autosomal dominant disorder caused by an abnormality of chromosome 17 and characterized by multiple skin tumors and abnormal cutaneous pigmentation,[1,2] with incidence of 1 in 2500–3000 births.[3] In patients with NF1, vascular abnormalities such as occlusion or stenotic disease, aneurysms, arteriovenous malformations and arteriovenous fistulas, are known to occur.[4] Because of the complex nature of the lesions, treatment options are limited and carry significant risk of bleeding. We report the case of a patient with NF1 who underwent coil embolization of the ruptured intercostal arteriovenous fistulas.

## CASE REPORT

A 47 year-old man with NF1 presented to our hospital complaining of sudden back pain. His past medical history was significant for right hemothorax of unknown cause 10 years prior to admission. A general examination revealed cutaneous neurofibroma and café-au-lait spots all over in his body. A contrast-enhanced thoracic computed tomography showed hematoma in the posterior mediastinum and leakage of the contrast material (**Fig. 1**). Rupture of the thoracic aorta was suspected, and an emergency angiogram was performed.

Digital subtraction angiogram (DSA) performed in the right transfemoral route revealed aneurysmally dilated intercostal arteries at the T9 to T11 level of the right side of the descending aorta and extravasation of the contrast media. Angiography of the T7, T8, T9, T10 intercostal arteries on the right side showed arteriovenous fistulas (**Fig. 2A**) and aneurysm (**Fig. 2B**). These ultimately drained into the azygous veins (**Fig. 3A**). Angiography of the right T11 intercostal artery demonstrated ruptured intercostal arteriovenous fistulas and aneurysm (**Fig. 3B**). Retrograde filling of the internal vertebral plexus and ascending lumbar veins were also seen.

Under local anesthesia, using Seldinger technique and the right femoral approach, a 5-French long sheath (Hanaco Medical, Tokyo, Japan) and a 5-French SHK, B1 catheter (Hanaco Medical, Tokyo, Japan) were placed. A microcatheter/guidewire (Cook, Bloomington, IN, U.S.) was advanced into the 8th to 11th intercostal artery. The intercostal arteriovenous fistulas and aneurysms were occluded with a total of 48 coils (1 of 30 × 4 mm, 3 of 20 × 3 mm, 1 of 40 × 5 mm; Trufill occlusion system, Johnson and Johnson, Tokyo, Japan, 11 of 5 × 2 mm, 3 of 6 × 2 mm, 6 of 4 × 2 mm, 5 of 3 × 4 mm, 11 of 3 × 5 mm, 6 of 3 × 2 mm; Cook, Bloomington, IN, U.S., 1 of 6 × 40 mm, and 1 of 5 × 50 mm platinum microcoil; Cook, Bloomington,

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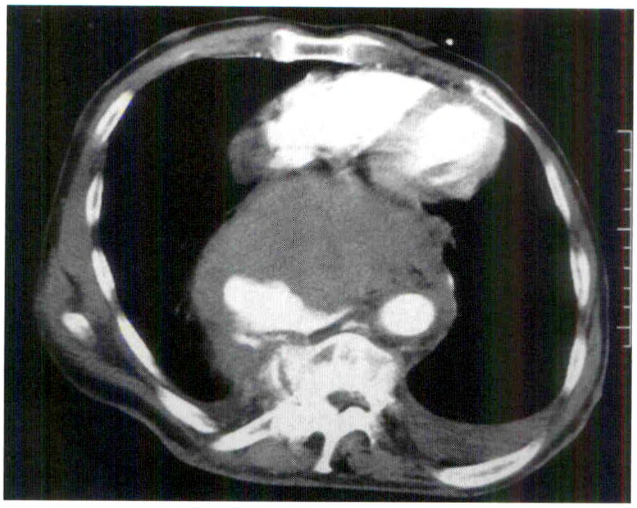

**Fig. 1** A contrast-enhanced thoracic computed tomography shows hematoma in the posterior mediastinum and contrast extravasation.

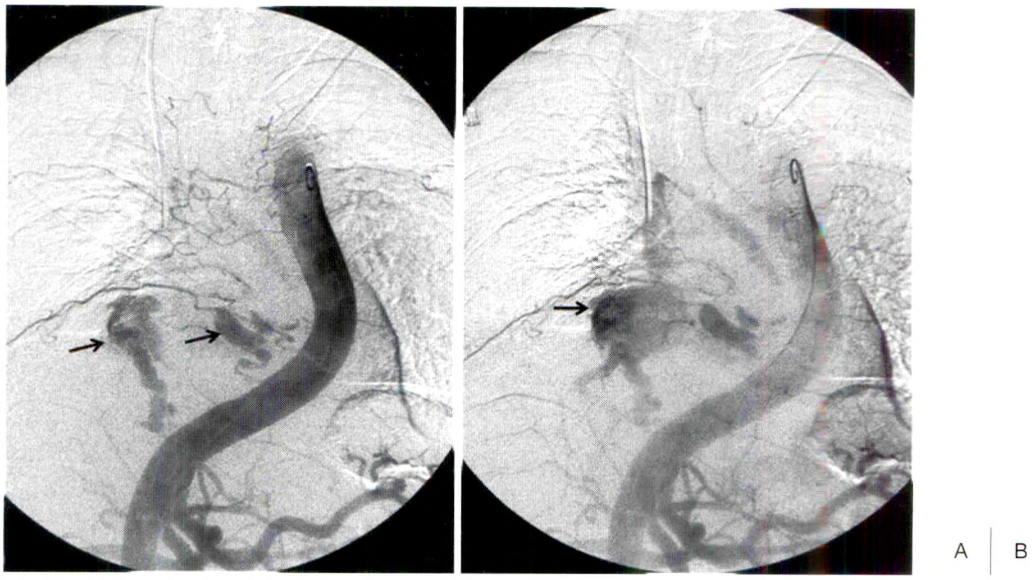

**Fig. 2** Thoracic angiography in early arterial phase reveals arteriovenous fistulas (arrow) from the right 7th through 10th intercostal arteries (**A**). Late phase shows the ruptured aneurysm (arrow) (**B**).

IN, U.S.). The post-embolization angiogram showed successful occlusion of the arteriovenous fistulas (**Fig. 3C**). The post-procedural course was uneventful. The follow-up CT on the 8th post-embolization day showed no change in size of the hematoma in the posterior mediastinum. Rebleeding was not seen, and the patient was discharged home in good condition.

## DISCUSSION

The incidence of vascular lesion in NF1 has been reported to be only 3.6%.[5] However, the frequency of blood vessel involvement in NF1 has been underestimated, primarily because lesions may be clinically silent or may be attributed to other causes once discovered.[1] There has been an increasing awareness of vascular

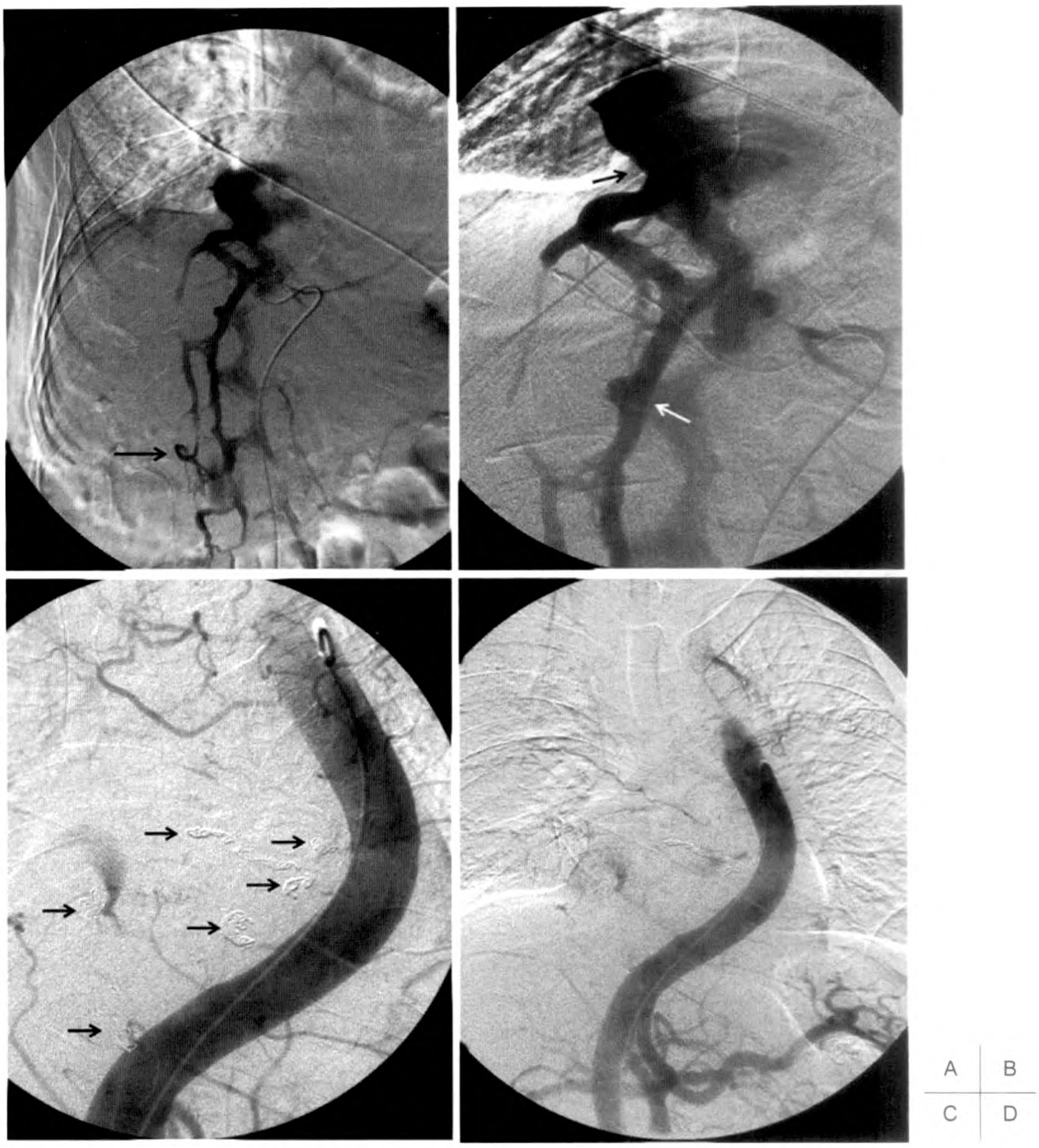

**Fig. 3** Late venous phase shows the azygos vein (arrow) (**A**). Selective angiography in venous phase of the right T11 intercostal artery shows the ruptured aneurysm (black arrow). White arrow indicates draining vein (**B**). Thoracic aortography after occlusion of feeders with microcoils (arrows) (**C**) shows no residual filling of feeding arteries (**D**).

lesions in patients with NF1, including stenosis, aneurysms and arteriovenous fistulas.[6] Arterial lesions seen in NF1 may include compression due to an extrinsic adjacent tumor, intramural thickening, and saccular or fusiform aneurysms due to vascular dysplasia of various types.[1]

Only a few cases of NF1 associated with ruptured intercostal arteriovenous fistula have been reported. Massive hemorrhage in patients with NF1 is a rare but potentially a lethal complication, and the prognosis is poor if the patient falls into hypovolemic shock.[2] Conventional treatment of intercostal arteriovenous fistulas is ligation of the feeding artery by open surgery. However, surgical treatment in patients with NF1 can be dangerous or even impossible because the natural history of this disease process is still not completely understood, and vascular fragility might exacerbate bleeding. Possible causes of bleeding in NF1 patients include bleeding by vascularized tumors of mesenchymal origin, such as ganglioneuromas or neurofibromas, and bleeding caused by rupture of weak medium in large caliber arteries.[3] These arteries are either surrounded by neurofibromatous or ganglioneuromatous tissue or have weak walls caused by intimal proliferation, thinning of the muscle layer, and fragmentation of the elastic layer, thus making them susceptible to aneurysm formation.[3)]

Endovascular treatment of vertebral arteriovenous fistula and hemothorax in NF1 has been reported in the literature.[1,4–10)] Coil embolization is a popular, less invasive, and safe method for the control of arterial hemorrhage in cases not requiring preservation of arterial flow.[9,10)] In order to find the source of bleeding, the best option is to make a radiological exploration, which allows the vascular surgeons to evaluate the individual lesions meticulously, with special attention to flow patterns. In our case, bleeding was due to a rupture of the intercostal arteriovenous fistula at T11 level producing posterior mediastinal hematoma. Endovascular coil embolization was successfully carried out in the management of the ruptured intercostal arteriovenous fistulas. Although good prognosis of endovascular treatment compared with surgery has been reported in the literature, fatal rebleeding remains a life-threatening complication. A well-developed tortuous vasculature structure in NF1 patients with vascular lesions can complicate endovascular treatment.[10)]

Percutaneous endovascular embolization of the intercostal arteriovenous fistula offers a new, radical and effective option. It is less invasive and allows precise and selective occlusion of only the abnormal vascular structures.

In conclusion, this is a rare case of ruptured intercostal arteriovenous fistulas in NF1, which were successfully treated with endovascular technique. Endovascular approach can be safe and effective in treating a lesion that may have otherwise been fatal.

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**Third Asian PAD Workshop**

# Treatment of PAD in Diabetes Mellitus Patients

October 8th, 2011
Gyeongju, Korea
Chairmen: Dr Hiroshi Shigematsu (Tokyo, Japan) and
Dr Bo Yang Suh (Daegu, Korea)

The Third Asian PAD Workshop was an important and successful medical education event sponsored by Astellas Pharma. The workshop featured an expert faculty of internationally renowned physicians active in the treatment and investigation of peripheral artery disease (PAD). This condition exacts a substantial toll in terms of mortality, morbidity, quality of life and healthcare costs. It is also a clinically valuable "window" through which to observe the extent of a patient's systemic atherosclerosis. As populations age and as the type 2 diabetes epidemic increases, the early detection and timely management of PAD is likely to gain considerable importance. This workshop builds on the success of the previous Asian PAD Workshops (in Jeju, 2009 and Osaka, 2010) in helping to establish the importance of early intervention and individualised therapy to achieve the best patient outcomes possible.

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## An Introduction: the Current Situation of Asian PAD

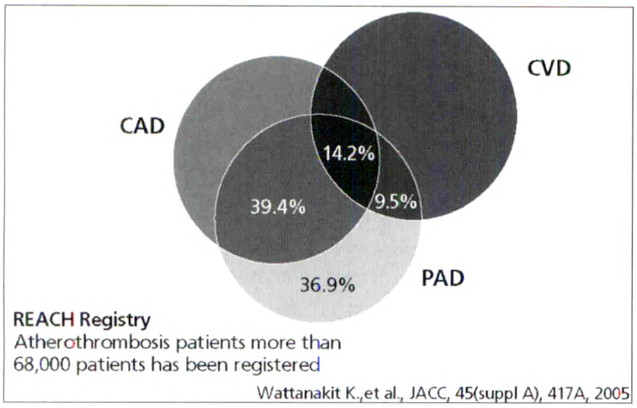
Dr Hiroshi Shigematsu
(Tokyo, Japan)

Atherosclerotic arterial disease is a progressive condition that causes ischaemic symptoms in various organs. PAD is now recognized as a valuable "window" through which to observe the extent of a patient's systemic atherosclerosis. Japan's aging population is set to increase significantly in the next 30 years. The number of patients with diabetes in Japan has increased at a surprising rate in the last ten years; from 7 million in 1997 to 9 million in 2007, and more than 20 million when patients with borderline diabetes were included.

There are a range of factors which contribute to this rapid change in PAD profile seen in Asian countries. Changes in lifestyle, for example car use or westernized living style which promote a lack of exercise, and improving nutrition all lead to increases in the incidence of diabetes mellitus and dyslipidemia.

Objective assessment of the severity of ischaemia in the

| | |
|---|---|
| **1954** | **Fontaine's classification**<br>Stage II: Intermittent claudication<br>Stage III: Rest pain<br>Stage IV: Ulceration, gangrene |
| **1981** | **Ad hoc Committee definition of limb-threatening ischaemia**<br>Ankle pressure <40 mmHg with rest pain<br>Ankle pressure <60 mmHg with ulcers or gangrene |
| **1986** | **SVS and ISCVS recommendation**<br>Ankle pressure <40 mmHg with rest pain<br>Ankle pressure <60 mmHg with ulcers or gangrene<br>Toe pressure <30 mmHg |
| **1989** | **European Consensus Document**<br>Rest pain, ulcers, or gangrene with ankle pressure <50 mmHg or toe pressure <30 mmHg |
| **1992** | **Second European Consensus Document** |
| **1997** | **Revised version of SVS recommendation** |
| **2000** | **Trans-Atlantic Intersociety Consensus (TASC)** |
| **2007** | **TASC II** |



**REACH Registry**
Atherothrombosis patients more than 68,000 patients has been registered

Wattanakit K.,et al., JACC, 45(suppl A), 417A, 2005

**Fig. 1** Overlap in Vascular Disease affecting different territories.

extremities has been focused on increasingly over the last 30 years. Decades of progress in classification and consensus and cooperation between medical and surgical vascular, cardiovascular, vascular radiology and cardiology societies across the world has been undertaken to address this issue, as follows:

TASC II was published in 2007 with goals to focus on key aspects of diagnosis and management, and to update the information based on new publications and the newer guidelines.[1,2]

### *REACH Registry*

Following the TASC II publication the **RE**duction of **A**therothrombosis for **C**ontinued **H**ealth (REACH), a large-scale international observational study of patients with or at risk of atherothrombosis from 44 countries involving 68,000 patients was undertaken.[3] The REACH Registry provides an opportunity to better understand the prevalence and clinical consequences of atherothrombosis in the outpatient setting in a wide range of patients from different parts of the world. The primary objective of REACH was to explore the impact of both classic and new risk factors on the prevalence of cardiovascular (CV) ischaemic events among patients with, or at high risk for, atherothrombotic disease. Results show there is a range of overlap in disease in the three territories of coronary, cerebral and PAD. Of those patients identified with symptomatic PAD, 40% had concomitant coronary disease, 10% had concomitant cerebrovascular disease and 14% had both (**Fig. 1**). Thus in PAD, ~65% of patients will have clinical evidence of other vascular disease. Results also suggest atherothrombotic conditions are more common in PAD patients.

Atherothrombosis constitutes disruption of the atherosclerotic plaque with superimposed thrombosis and is the common pathophysiological mechanism underlying cerebrovascular disease (CVD), coronary artery disease (CAD) and PAD. The atherosclerotic and thrombotic processes are interdependent.[4] CVD includes ischaemic stroke and/or transient ischaemic attack (TIA), CAD includes myocardial infarction (MI), angina pectoris (stable, unstable) and sudden death and PAD includes intermittent claudication, critical limb ischaemia, gangrene and necrosis. The presence of atherothrombotic risk factors, as outlined in **Table 1**, can increase the risk of events in asymptomatic people.

### *AtheroThrombosIS (ATIS)*

ATIS is the most common cause of death in high-income and middle-income countries. According to the World Health Organization (WHO), in 2004 atherothrombosis was the leading cause of death worldwide with 22% of all deaths attributed to atherothrombosis.[6] Atherothrombosis significantly shortens life expectancy; results of the Framingham Heart Study show that males aged 60 years with a history of any CVD has life expectancy reduced by −7.7 years, history of acute MI by −9.2 years and history of stroke by −12.0 years.[7] So PAD patients are at increased risk of cardiovascular ischaemic events. Five-year outcomes for PAD patients ≥50 years include the following scenarios:

- Limb morbidity 70–80% stable claudication, 10–20% worsening claudication, and 1–2% critical limb ischaemia;
- CV morbidity, 20% nonfatal CV event such as MI or stroke;
- Mortality ~15–30% with 75% from CV causes.[8]

When 1 year CV event rates are considered as a function of the number of symptomatic disease locations, the risk of major adverse cardiovascular event increases with increased symptomatic arterial bed involvement.[9]

### *Regional differences*

Interestingly, there are differences in disease outcomes for patients in different countries. Cardiovascular and limb event rates differed in Asian PAD patients from those of other regions of the world. Rates of cardiovascular death, non-fatal myocardial infarction and stroke, leg revascularization and amputation were lower in Asian countries. At a 3 year follow up, vascular death rate was similar in Asia to other regions, while it was significantly lower in Japan and Australia. MI, stroke and vascular death rates were also low in Japan compared to other regions including other Asian countries.

A 1 year follow up of the REACH registry patients found that non-fatal stroke is highly prevalent in CVD patients compared

**Table 1.** **Atherothrombotic risk factors**[5]

| Major | Minor |
|---|---|
| Type 1 or 2 diabetes − under drug treatment | Systolic blood pressure ≥ 150 mmHg, despite therapy for at least 3 months |
| Diabetic nephropathy | Primary hypercholesterolemia |
| Ankle brachial index <0.9 | Current smoking >15 cigarettes per day |
| Asymptomatic carotid stenosis ≥ 70% | Male ≥ 65 years; female ≥ 70 years |
| Evidence of at least 1 carotid plaque | |

**Table 2. Drugs for use in PAD patients in Japan**

| Drugs for PAD Patients in Japan | |
|---|---|
| Cilostazol | Eicosapentanoeic acid |
| Aspirin | Algatroban |
| Ticlopidine or clopidogrel | Lipid-lowering drugs |
| Sarpogrelate | Other pharmaceutical agents |
| Prostaglandins: | |
| a. limaprost ($PGE_1$) | |
| b. alprostadil (PGEI, lipo-$PGE_1$) | |
| c. beraprost ($PGI_2$) | |

to other registered groups of CAD or PAD patients. In global patients, the incidence of stroke event in PAD patients was the same as in CAD patients.9) In contrast, in Japan non-fatal stroke was highly prevalent in PAD patients compared to global patients.10) Prevention of stroke is mandatory in the long-term treatment for the Japanese PAD patients. Improved medical care systems and social environment may account for the differences seen.

*5 Year Survival*

In Japan, 5 year survival rates of PAD patients (60–70%) are worse than breast cancer (85%) and similar to colon cancer (68%). In a prospective cohort study of patients aged over 65 years with monitored follow-up over 5 years, compared with patients without PAD, those with asymptomatic PAD or symptomatic PAD had a significantly increased risk of mortality or vascular morbidity.11)

The ACCF/AHA recently (2011) revised the guidelines for the management of PAD.12) It states that the resting ankle brachial index (ABI) be used to establish the lower extremity PAD diagnosis in patients with suspected lower extremity PAD, defined as individuals with >1 of the following: exertional leg symptoms, non-healing wounds, aged ≥65 years or ≥50 years with a history of smoking or diabetes. ABI results should be uniformly reported with non-compressible values defined as >1.40, normal values 1.00 to 1.40, borderline 0.91 to 0.99 and abnormal ≤0.90. ABI is easily measured using the Form machine which is widely used throughout Japan.

*From TASC II to TASC III*

In recent years new data has emerged leading to the revision of TASC II to TASC III. The Japanese Circulation Society Guidelines for management of Peripheral Arterial Occlusive Disease were published in 2009. It states that the purpose of medical therapies is to improve ischaemic symptoms, to improve patency for vascular reconstruction including endovascular treatment and to prevent systemic vascular event.

*Drugs used in PAD*

Prostaglandin is still one of the most commonly used drugs for PAD patients in Japan (**Table 2**)13). The prostaglandin beraprost sodium is believed to have dual effects in PAD. It improves ischaemic symptoms by increasing blood flow via vasodilation and helps to prevent future CV events via inhibiting progression of arteriosclerosis.

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# PAD in Thai Diabetic Patients

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PAD is more common and diffuse in diabetics than non-diabetic patients. If diabetic patients have concomitant CV disease then the prevalence of PAD is markedly increased. The prevalence of PAD in Thai type 2 diabetes (T2DM) patients has been established in several multicentre studies, most notably in the 2003 PAD-SEARCH study.1)

*Pad-Search Study*

PAD – SEARCH (SEARCH: Screening & Evaluation of diabetic patients in Asia Regions for Characteristics by High Risk Factors). The objective of PAD-SEARCH was to identify the PAD risk factors in diabetic patients and investigate the prevalence of PAD in diabetic patients with identified risk factors. PAD-SEARCH was a multinational cross-sectional study with inclusion criteria to include diabetes patients ≥50 years, diabetes patients with ≥1 risk factors (i.e., smoking, hypertension, dyslipidaemia). Clinical sample n = 7,300 (n = 6,771; ♂ = 2,987, ♀ = 3,784) with 15 sites across Asia. The definition of abnormal outcome variables was based on VS-1000 measurements, with abnormal values being ABI value <0.9, baPWV value 1400~1800 cm/sec.

Results show that the incidence of PAD in the Thai T2DM patients was 15.9%, which is consistent with other countries in Asia (**Fig. 1**). Key factors identified as associated with increased risk of PAD in Thai diabetics are age (most important), duration of diabetes, female gender, current smoker, high blood lipids and hypertension.

*Treatment of Pad in Diabetes*

Medical and surgical treatment is available for symptomatic

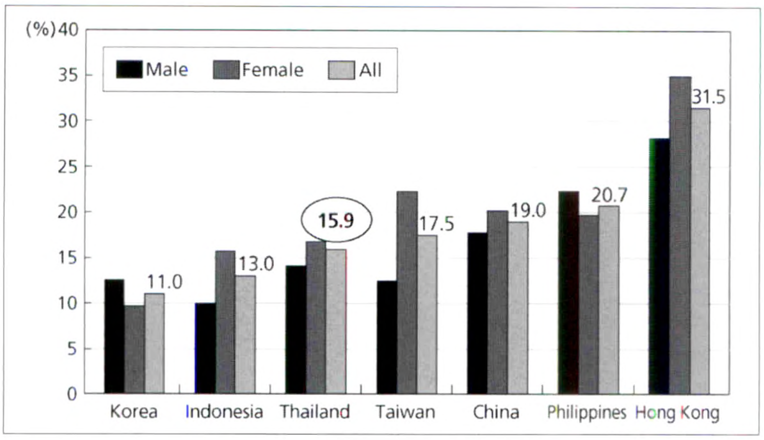

**Fig. 1** Unadjusted frequency of PAD by gender and country in Asian patient with T2DM.

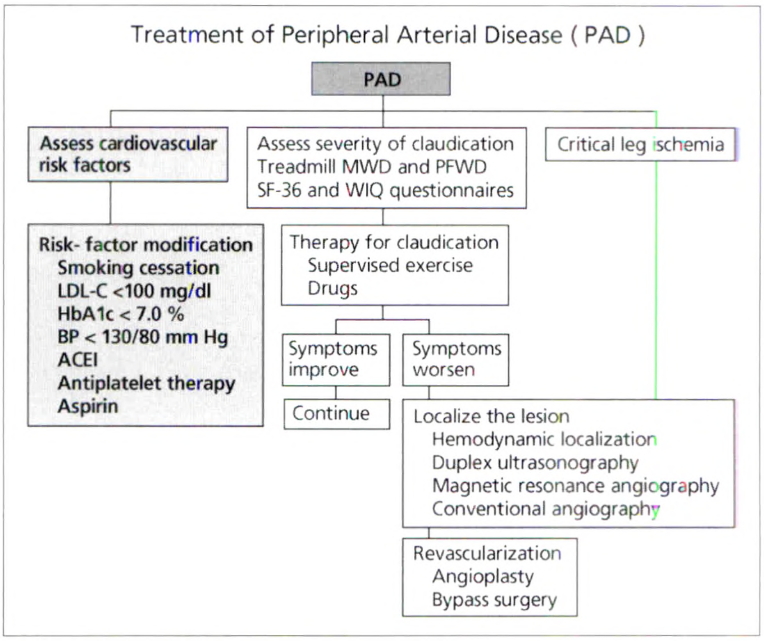

**Fig. 2** Treatment strategies for PAD.

PAD. To help prevent other atherosclerotic events patients should undertake smoking cessation, good glycaemic control, blood pressure control, lipid control, ACEI and antiplatelet therapy. **Figure 2** outlines the treatment strategy for use in assessing and treating PAD.

### *Exercise for Treatment of Claudication*

Nehler & Hiatt (1999) established that when patients followed exercise guidelines of claudication within 5 min, ex-rest-ex session 35 min, for 3–5 times/week they increased maximal treadmill walking distance by 179m.[2]

### *Drug Treatment of Claudication*

In a study conducted to compare cilostazol with placebo and pentoxifylline. Results showed that cilostazol significantly improved absolute claudication distances or maximum walking distances compared to groups that received pentoxifylline or placebo; pentoxifylline did not show any significant improvement in walking distances compared to placebo.[3]

In a separate double blind trial investigating the effect of beraprost on intermittent claudication, 549 patients with intermittent claudication were randomized to beraprost 40 µg TID or placebo and treated for 6 months. Results (**Fig. 3**) showed that pain-free walking distances increased by 81.5% and 52.5%, respectively, in the beraprost and placebo groups and maximum walking

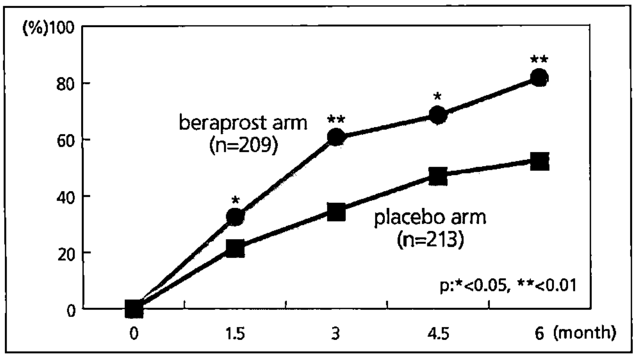

**Fig. 3** Change in pain-free walking distance from treadmill exercise tests with berapost vs. placebo.

distances by 60.1% and 35.0%, respectively; demonstrating that beraprost is an effective symptomatic treatment of patients with intermittent claudication.[4)]

*Drug Treatment for Cardiovascular Risk*

A study was undertaken to determine whether aspirin and antioxidant therapy, combined or alone, are more effective than placebo in reducing the development of cardiovascular events in patients with diabetes and asymptomatic PAD. No evidence was found of any interaction between aspirin and antioxidant and the results of this trial do not provide evidence to support the use of aspirin or antioxidants in primary prevention of cardiovascular events and mortality in the population with diabetes studied.[5)] These results are supported by those of Berger et al. (2009), which found that in patients with PAD the use of aspirin alone or in combination with dipyridamole resulted in a statistically non-significant decrease in cardiovascular events, although a significant reduction in non-fatal stroke was seen.[6)]

A meta-analysis of placebo-controlled, Japanese randomized trials was conducted to evaluate the effect of beraprost sodium on the vascular events occurring in patients with PAD. Two trials met the criteria, each of which was a comparative trial of beraprost (40 µg t.i.d.) and placebo (t.i.d.), with a six-month follow-up period. With both trials combined, the analysis included 594 patients in the beraprost group and 590 in the placebo group. The risk ratio was 0.608 (95%CI: 0.41 to 0.90, $P = 0.012$), demonstrating the efficacy of beraprost on all vascular events. The risk ratio for lower limb deterioration was 0.598 (95% CI: 0.34 to 1.06, $P = 0.079$), which was similar to that for all vascular events. A similar result was also obtained for cardio/cerebrovascular events. When data are combined for exacerbation of leg symptoms and cardio/cerebrovascular events there was a 39% reduction with beraprost vs. placebo.[7)]

In summary, it is important to diagnose PAD in diabetes to prevent disability and limb loss, and to identify a patient at high risk of MI, stroke and death. Screening should be undertaken in any patient with symptoms of PAD or non-palpable pedal pulses, all patients ≥50 years of age and patients <50 years with vascular risk factors (smoking, hypertension, dyslipidaemia, duration of diabetes >10 years). ABI should be used for screening, and <0.9 is indicative of a diagnosis of PAD.

Systemic atherosclerosis should be treated intensively, patients must not smoke, have good glycaemic control, ACE-Inhibitor, statin, aspirin or other antiplatelet therapy. In the case of symptomatic PAD patients should undertake exercise rehabilitation in all cases and consider pharmacologic therapy. Beraprost effectively reduces the risk of vascular events in patients with PAD. Preventative foot care programs are of value and revascularization should be considered in cases with non-healed ulcer or gangrene, disabling claudication refractory to conservative therapy and rest pain.

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## The Epidemiology and Treatment of PAD in Japanese Diabetic Patients: the Kyushu Prevention Study for Atherosclerosis (KPSA)

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The KPSA aimed to evaluate the usefulness of brachial-ankle pulse wave velocity (baPWV), a noninvasive marker for arterial stiffness, in high risk patients of atherosclerosis. Whether baPWV is a useful predictive maker for cardiovascular events in patients with diabetes has not been established. The KPSA evaluated the benefit of baPWV for the prediction of cardiovascular morbidity and mortality in diabetic subjects.[1)]

The KPSA established the prevalence of PAD in 3,906 Japanese patients with diabetes evaluated by ABI measurement. Subjects were outpatients with diabetes (n = 4,249). Baseline ABI was measured using a device "form PWV/ABI (Omron-colin Co. Ltd., Japan)." Valid information was available for 3,906 diabetic patients (mean age: 60.8 years) including 1,612 elderly patients (>65 years). Lower ABI of <0.9 was considered diagnostic of PAD.

The frequency distribution of lower ABI in all diabetic subjects shows that in the KPSA, ABI <0.9 is 295 (7.6%). This means that 1/13 diabetic patients in this study has PAD. Borderline PAD (0.9–1.0) was 10.7%. Taken together, 16.4% patients had an ABI of <1.0 (with these patients suspected of having PAD) (**Fig. 1**).

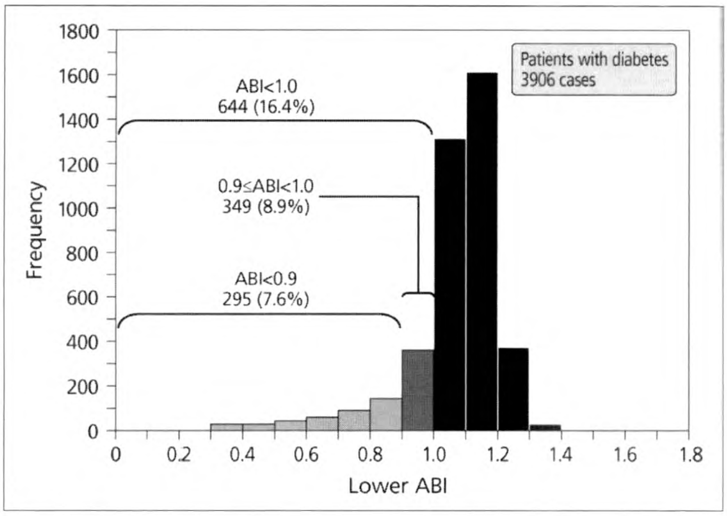

**Fig. 1** Frequency distribution of lower ABI in all diabetic subjects.

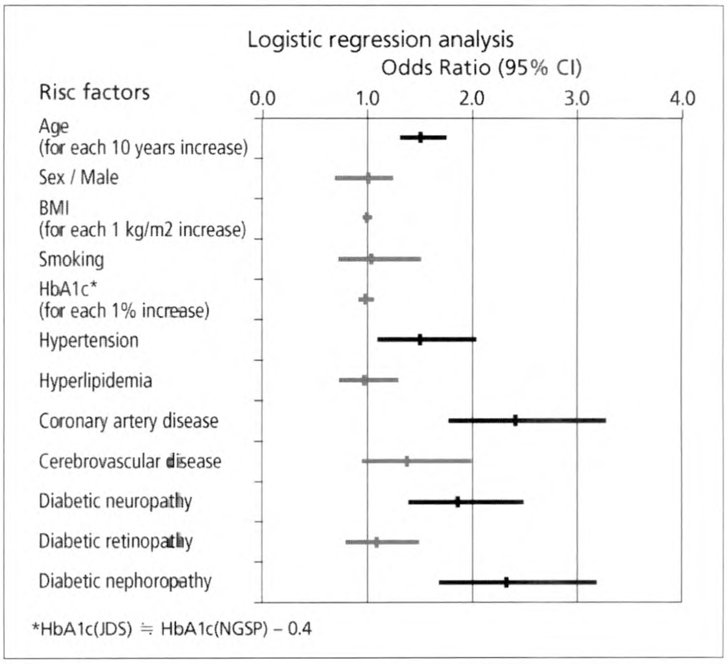

**Fig. 2** Risk factors for PAD (all diabetic subjects).

Elderly patients (>65 years) had a much higher prevalence of PAD than younger patients; the incidence of ABI of <1.0 was 377, 23.4% of elderly patients.

When the rate of previous diagnosis and treatment in PAD patients was investigated it was found that previous diagnosis of PAD before the enrollment to KPSA was only 24.4% in subjects with a low ABI (<0.9). Prior to the KPSA, only 45.1% of patients diagnosed with low ABI had previously been treated with any anticoagulant or platelet inhibitor because of atherosclerotic diseases. When the rate of previous diagnosis in accordance with the severity of ABI was classified, it was confirmed that no more than 20% of low ABI subjects in relatively mild ABI deterioration had been previously diagnosed with PAD. Furthermore, the rate of previous diagnosis even in the ABI group with the most severe deterioration was 50%. The rates of previous treatment in PAD patients were similar to diagnosis rates suggesting that a high proportion of PAD patients with diabetes had not been given the benefit of anticoagulant therapy, regardless of the severity of their ABI deterioration.

Risk factors for PAD were evaluated; in all subjects (**Fig. 2**), aging, hypertension, CAD, neuropathy and nephropathy were significant explanatory variables, whilst results in elderly diabetic patients were very similar with aging, hypertension, CAD, CVD and nephropathy being the greatest risk factor to PAD in

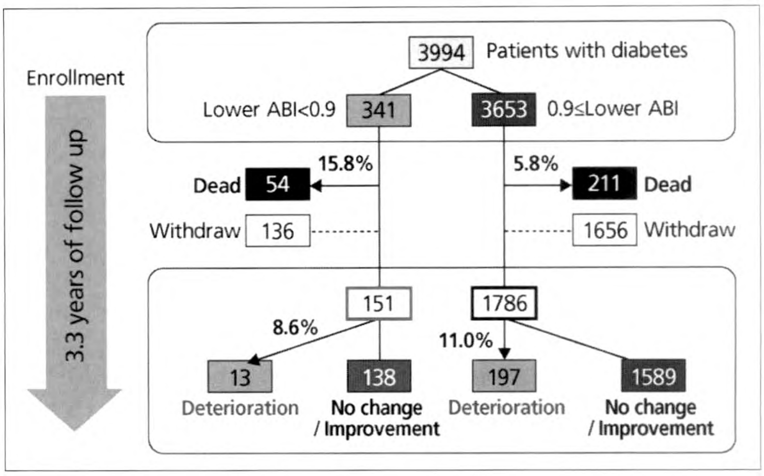

**Fig. 3** Outcomes of PAD patients with diabetes in KPSA.
KPSA: Kyushu Prevention Study for Atherosclerosis

**Table 1. Patient characteristics in the KPSA follow-up study**

| | Lower ABI <0.9 | | Lower ABI ≥0.9 | | |
|---|---|---|---|---|---|
| | Deterioration | No change/ improvement | Deterioration | No change/ improvement | P value |
| n | 13 | 138 | 197 | 1589 | |
| Age | 73.0 ± 7.5 | 68.2 ± 9.9 | 63.2 ± 12.7 | 61.0 ± 10.6 | <0.0001 |
| Gender (male) | 8 (61.5%) | 74 (53.6%) | 118 (59.9%) | 903 (56.8%) | 0.6956 |
| Smoking | 4 (30.8%) | 32 (23.2%) | 55 (27.9%) | 390 (24.5%) | 0.6773 |
| Hypertension | 10 (76.9%) | 102 (73.9%) | 117 (59.4%) | 799 (50.3%) | <0.0001 |
| Hyperlipidemia | 6 (46.2%) | 80 (58.0%) | 105 (53.3%) | 859 (54.1%) | 0.7514 |
| Retinopathy | 3 (23.1%) | 57 (41.3%) | 63 (32.0%) | 403 (25.4%) | 0.0003 |
| Nephropathy | 5 (38.5%) | 50 (36.2%) | 72 (36.6%) | 317 (20.0%) | <0.0001 |
| Neuropathy | 4 (30.8%) | 57 (41.3%) | 63 (32.0%) | 364 (22.9%) | <0.0001 |
| BMI | 23.4 ± 3.1 | 24.0 ± 3.6 | 24.6 ± 4.2 | 24.4 ± 3.9 | 0.4071 |
| HbA1c (%) | 8.8 ± 2.0 | 7.7 ± 1.9 | 8.1 ± 2.0 | 7.6 ± 2.0 | 0.0024 |

diabetic elderly patients.

The KPSA patients entered a 3.3 year follow-up stage (**Fig. 3**). During the follow up period 54 patients (15.8%) with low ABI died and the condition of 8.6% of 151 survivors had deteriorated. In contrast, 211 (5.8%) patients with ABI >0.9 had died and the condition of 11% of 1,786 survivors had deteriorated.

As shown in **Table 1**, differences were seen between those patients who showed health deterioration and those who's condition remained the same or improved during follow-up.

When risk factors for the deterioration of ABI in diabetic patients were evaluated, aging, neuropathy and, interestingly, HbA1c at baseline were found to be significant explanatory variables.

The KPSA therefore found that Japanese PAD patients with diabetes have a high mortality. HbA1c and nephropathy were significantly correlated to the deterioration of ABI in these diabetic patients. This study suggests that treatment for PAD at all severity levels could prevent the further deterioration of ABI in diabetic patients.

*Prediction of Mortality and Cardiovascular Events by ABI*

In a summary of reports about predictive ability of ABI for future cardiovascular outcomes patients with low ABI were at twice the high risk of CAD and stroke and 4 times the high risk of all-cause mortality, rising to 6 times the high risk of cardiovascular mortality.[2)] The mortality and cardiovascular event risks in PAD patients from KPSA were analysed. Cause of death was compared between PAD and non-PAD subjects. It was shown that low ABI was a strong risk of all-cause mortality. Even after the adjustment by age, gender, BMI, hypertension, Smoking and HbA1c, low ABI remained ~twice risk of mortality. High PWV was also a significant predictor for all-cause mortality.

Finally, the cause of death in the KPSA was investigated. It was found that in all subjects, the distribution of cause of death was quite similar to that of the general population in Japan. Low ABI was a strong risk for mortality. Interestingly, the rate of infectious disease was increased in low ABI group. In contrast, however, the rate of cardiovascular deaths was markedly increased in the high PWV group.

To conclude, PAD is a high risk for all-cause mortality in Japanese patients with diabetes. Not only cardiovascular deaths but also infectious diseases should be given attention in PAD patients with diabetes. As the measurement of ABI is convenient and non-invasive, it should be considered useful as a screening method of PAD in patients with diabetes. Increasing diagnostic efforts and intensive early treatments for PAD are needed to improve patients' quality and duration of life in Japanese diabetic patients.

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# Pharmacotherapy for Peripheral Artery Disease: A Vascular Surgeon's Perspective

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*Importance of Early Detection*

Peripheral artery disease is a leg disease that is often found among patients with diabetes, high blood pressure and hypercholesterolemia. The 5 year survival rate for PAD patients is 75%.[1] Statistics show that approximately 18% of diabetes patients have PAD.[2] The number of patients with diabetes is increasing with around 22 million Japanese (~17% of the Japanese population) now estimated to have diabetes or be at risk of diabetes. Similarly, the number of Chinese diabetes patients is estimated to be 92.4 million,[3] (7% of its population). These figures suggest that more than 4 million people in Japan and 16 million in China have PAD.

*Techniques for the Detection of PAD*

Clinician should examine whether the patient has any numbness, cold sensation or pain in their legs. The physician must check the condition of the patient's feet, and palpate the Dorsalis pedis artery (**Fig. 1-a**). It is important to examine and make sure that the pulse is strong; they should palpate the posterior tibial artery (**Fig. 1-b**), making sure that the pulse is strong again.

The examination for PAD is difficult to perform and not all hospitals have the necessary equipment. Doctors must at least interview and check their patients' legs, in particular, the feet. If any abnormality of the pulse is found or if PAD suspected, then a more detailed palpation should be performed. The full palpation examination is performed on four parts of the body. If the pulse is weak or if no pulse is felt, then PAD should be suspected. If some noise in the pulse is felt, it may suggest a narrowing of the vessel; in that case auscultation must be performed.

A more precise method than palpation for detecting PAD is the ABI, it is very simple and effective for PAD screening and can be easily achieved using an automatic instrument that measures ABI using the blood pressure of both arms and legs simultaneously (**Fig. 1-c**). An ABI <0.9 is considered to be abnormal and enables a diagnosis of PAD.

PAD remains one of the most under-diagnosed diseases of all cardiovascular disease so to improve the short- and long- term prognosis of patients early detection and optimal treatment is critical. In most cases, the presence of PAD is clarified by medical history and physical examination including palpation of arterial pulses and measurement of ABI without using any special medical appliances. It is therefore vital to start screening your at-risk patients using these methods. A significant difference can be made by helping to modify patient risk factors.

*Two Goals for the Treatment of PAD*

Peripheral arterial disease, an occlusive disease of the arteries of the aorta, iliac, and lower extremities, is a common manifestation of systemic atherosclerosis.[4] Medical therapies for PAD aim to improve the symptoms of the lower leg and to prevent cardiovascular events (**Fig. 2**).

Intermittent claudication is defined as fatigue, discomfort, or pain that occurs in specific limb muscle groups during effort due to exercise-induced ischemia. The severity of the symptoms can be classified according to the Fontaine category (**Table 1**).[5] Stage II represents the most common symptom, while stages III and IV are more frequent in patients with diabetes and dialysis.

Most PAD patients do not need invasive treatment.[6] Key treatments for patients with claudication are reducing modifiable atherothrombotic risk factors and symptomatic relief via supervised exercise programs and/or pharmacotherapy. Exercise conditioning, especially with supervised, structured regimens, increases pain-free and maximal walking time and distance, with average improvements of 134% to 179% for pain-free walking and 96% to 122% for maximal walking ability.[7–10]

Only cilostazol is recommended for the treatment of PAD by TASC II and ACC/AHA Guidelines. However, drugs available for treatment in Asia are different from U.S. and Europe, and this needs to be taken into consideration in the pharmacotherapy of PAD. A large variety of oral drugs for PAD are commercially available in Japan (**Table 2**).

*Review of Evidence from Clinical Studies*

In eight randomised, double-blind, placebo-controlled trials, which included 2,702 patients with stable, moderate to severe claudication, cilostazol therapy increased maximal and pain-free walking distances by 50% and 67%, respectively, without major

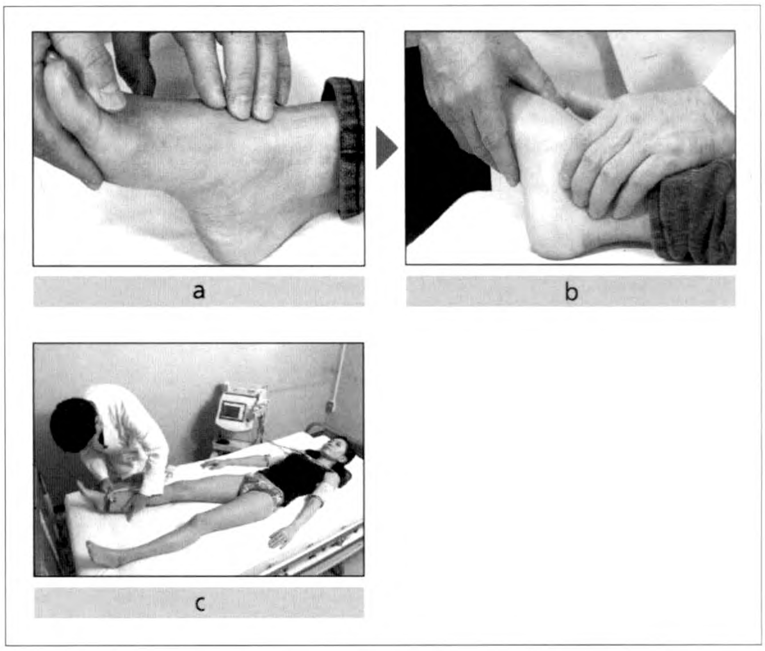

**Fig. 1** Detection of PAD.

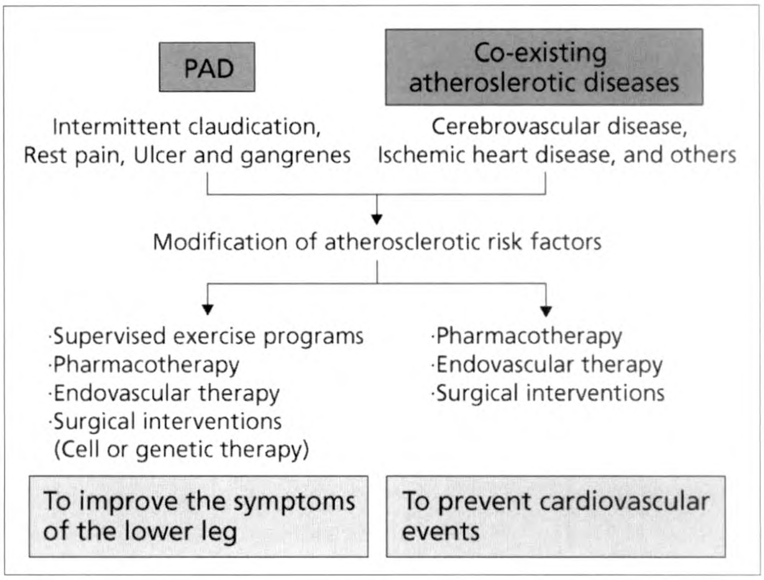
PAD
Co-existing atheroslerotic diseases
Intermittent claudication, Rest pain, Ulcer and gangrenes
Cerebrovascular disease, Ischemic heart disease, and others
Modification of atherosclerotic risk factors
·Supervised exercise programs
·Pharmacotherapy
·Endovascular therapy
·Surgical interventions
(Cell or genetic therapy)
·Pharmacotherapy
·Endovascular therapy
·Surgical interventions
To improve the symptoms of the lower leg
To prevent cardiovascular events

**Fig. 2** Two goals for the treatment of PAD.

adverse effects. In addition, quality of life assessments revealed enhanced scores for physical well-being.[11]

Another randomized controlled trial of beraprost sodium conducted in Europe in patients with intermittent claudication showed pain-free walking distances increased by 81.5% and 52.5%, respectively, in the beraprost and placebo groups ($P$ = 0.001) and maximum walking distances by 60.1% and 35.0%, respectively ($P$ = 0.004). The incidence of critical cardiovascular events was 4.8% in the beraprost group and 8.9% in the placebo group.[12]

**Table 1. Classification of PAD: Fontaine's stages[5]**

| Stage | Clinical |
|---|---|
| I | Asymptomatic |
| IIa | Mild claudication |
| IIb | Moderate-severe claudication |
| III | Ischaemic rest pain |
| IV | Ulceration or gangrene |

**Table 2. Oral drugs available for the treatment of PAD in Japan**

| Drug | Pharmacologic action |
|---|---|
| Ticlopidine hydrochloride | Inhibitor of ADP-stimulated platelet aggregation |
| Cilostazol | PDE 3 inhibitor |
| Limaprost alfadex | Prostaglandin $E_1$ analogue |
| Beraprost sodium | Prostacyclin analogue |
| Eicosapentanoic acid | Inhibitor of $TXA_2$ production |
| Sarpogrelate hydrochloride | $5\text{-}HT_2$ receptor antagonist |
| Aspirin* | COX inhibitor |

*Aspirin is not approved for PAD but commonly used in Japan

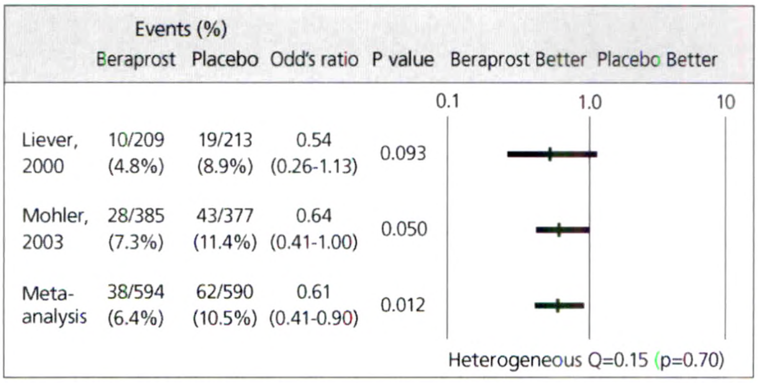

**Fig. 3** Beraprost significantly prevented cardiovascular events.

However, in another clinical trial conducted in patients with intermittent claudication in the U.S., there was no significant improvement in maximum walking distance in the beraprost group (16.7%) as compared with the placebo group (14.6%, *P* = NS). Administration of beraprost in this study did not improve the pain-free walking distance, and there was no improvement in the quality-of-life measures between the treatment groups.[13)]

Ticlopidine significantly improved mean walking distance in two clinical trials. In a multicenter trial of patients with chronic intermittent claudication ticlopidine had a beneficial effect both in the treatment of the symptoms and the prevention of vascular complications in patients with intermittent claudication.[14)]

In another study patients with intermittent claudication were randomly allocated to receive the antiplatelet agent ticlopidine (250 mg twice per day) or an identical placebo. Long-term treatment with ticlopidine improved walking ability and ankle systolic blood pressure in patients with claudication.[15)]

Cilostazol, beraprost and ticlopidine have been studied for their ability to prevent cardiovascular events in PAD patients.[14,15)] Cilostazol did not prevent death and cardiovascular events. There was no significant difference in all death and cardiovascular events between the placebo and cilostazol groups.[16)] However, meta-analysis of randomized controlled trials demonstrated that beraprost significantly prevented cardiovascular events (**Fig. 3**).[17)] Similarly, ticlopidine significantly inhibited cardiovascular events in 169 patients with chronic intermittent claudication due to obstructive PAD in another trial. There was a significant difference in cardiovascular events between placebo and ticlopidine groups.[18)]

It is important to note that contraindications, warnings and precautions from respective drug package inserts reveal significant potential limitations relating to the use of oral PAD drugs which must also be taken into consideration when planning treatment.[19)] For example, patients with congestive cardiac failure, tachycardia, ischaemic heart disease, severe renal disease and diabetes mellitus are suitable for treatment with beraplost. These diseases are frequently concomitant with PAD.

All of these considerations are reflected in the current strategy in Japan for the oral pharmacotherapy of PAD (**Fig. 4**).[20)] This strategy takes into account the fewer contraindications, warnings and careful administration requirements for beraprost compared with both cilostazol and ticlopidine. Beraprost therefore plays a key role in the improvement of lower leg symptoms and the prevention of cardiovascular events. Where tolerated, aspirin is recommended to be used as a base-line drug in all cases.

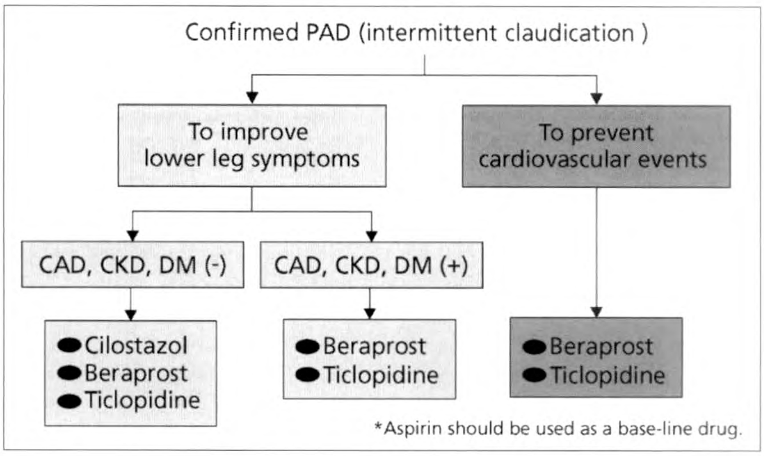
Confirmed PAD (intermittent claudication )
To improve lower leg symptoms
To prevent cardiovascular events
CAD, CKD, DM (-)
CAD, CKD, DM (+)
●Cilostazol
●Beraprost
●Ticlopidine
●Beraprost
●Ticlopidine
●Beraprost
●Ticlopidine
*Aspirin should be used as a base-line drug.

**Fig. 4** PAD pharmacotherapeutic strategy: choice of oral drugs.

*Beraprost: Has the Highest Usage Rate in the J-Method Study*

J-Method is the **J**apan **Me**dication **Th**erapy f**o**r peripheral arterial **D**isease. In 2006, the J-Method study group initiated a prospective observational cohort study to investigate the current status of PAD drug treatment in Japan, and the effects of drug treatment, risk factors, and complications on disease progress and onset of cardiovascular events in PAD patients. Results were published in April 2010.[21)]

Of 625 PAD patients recruited (with ankle-brachial index [ABI] of <0.9, subjective symptoms of PAD and a history of vascular reconstruction of the lower limbs), 557 were followed up for 3 years; their PAD treatment, risk factors and cardiovascular events were monitored (Fontaine classification and ABI).

Three drugs – beraprost sodium, cilostazol and aspirin – were the most frequently used treatments and most patients received two oral drugs in combination. At the time of enrollment, most patients (43%) received beraprost followed by cilostazol (40%) and aspirin (31%). After 3 years, most patients (32%) still received beraprost.

In the top three drugs with the highest usage rate (i.e., beraprost, cilostazol and aspirin), for those patients group without a history of vascular reconstruction in the lower limbs, the ABI at the time of enrollment was compared with that at last evaluation. There was a significant improvement in ABI in the group treated with beraprost, but not in the group treated with cilostazol or aspirin.

Moreover, beraprost has been found to be suitable for patients with both PAD and diabetes mellitus.[21)] Beraprost may increase glucose uptake by skeletal muscle in patients with obesity and diabetes mellitus.[22)]

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# Impaired Insulin Signaling in the Endothelial Cells Reduces Insulin-induced Glucose Uptake by the Skeletal Muscle

Dr Tetsuya Kubota
(Tokyo, Japan)

In recent years there has been rapid growth in diabetes in Japan which now is one of the nations most affected by the worldwide diabetes epidemic.1) Currently around 22 million people have T2DM in Japan, representing a 35-fold increase in incidence since 1955. This burgeoning number of patients developing T2DM is a major threat to health. Diabetes magnifies the risk of CV morbidity and mortality, reflecting a growing epidemic of macrovascular complications, including diseases of the coronary arteries, peripheral arteries and carotid vessels. This high prevalence of T2DM is associated with a significant economic burden, with diabetes accounting for up to 6% of the total healthcare budget. The increasing incidence of T2DM is likely due to pathological processes (**Fig. 1**) in an ageing population exposed to the negative health effects of 'westernized' lifestyles, including diets high in fat (Japanese fat intake has increased 4-fold in 50 years) and carbohydrate combined with reduced levels of exercise.

Approximately only one third of patients with T2DM achieve the recommended target $\text{HbA}_1\text{C}$ of 6.5% for glycaemic control. Consequently, new insights into the pathological process are needed to provide novel treatment approaches that can help patients achieve greater glycaemic control and so prevent the long-term complications of T2DM.

### *Skeletal Muscle Plays an Essential Role in Insulin-Induced Glucose Uptake*

It is established that muscle insulin resistance precedes and causes both metabolic syndrome and T2DM, leading to macro- and microvascular diseases. Muscle is the organ with the largest glucose consumption. In order to stimulate insulin-induced glucose uptake by the skeletal muscle, insulin has to be delivered into the capillaries, and cross the endothelial barrier to enter the interstitial spaces.

Skeletal muscle is one of the major target organs of insulin actions and plays an essential role in insulin-induced glucose uptake.2,3) Insulin signaling in vascular endothelium produces at least two types of actions. First, insulin modifies endothelial homeostasis in arteries, thereby making the vascular wall less susceptible to atherosclerosis.4) Second, insulin may regulate its own delivery to skeletal muscle and other tissues.5,6) Indeed, evidence suggests that insulin delivery to skeletal muscle interstitium is the rate-limiting step in insulin-stimulated muscle glucose uptake and that this process is impaired in obesity.5)

Based on these observations, two models of skeletal muscle insulin resistance are proposed (**Fig. 2**). The first involves impairment of cellular signaling within the myocytes, while the second involves impairment of insulin delivery to skeletal muscle. Kubota and colleagues hypothesized that an insulin signaling defect in the endothelial cells impairs insulin-induced capillary recruitment and insulin delivery in the skeletal muscle in obesity.7)

To study whether insulin activates insulin signaling to facilitate its own transendothelial transport, Kubota and colleagues created and studied mice with knockout of IRS-2 (ETIrs2KO mice) in endothelial cells. Compared with controls, insulin-stimulated phosphorylation of Akt and eNOS was decreased in endothelial cells from ETIrs2KO mice. In addition, capillary recruitment was significantly impaired in the ETIrs2KO mice from 60 min onward after insulin infusion. The increase of interstitial

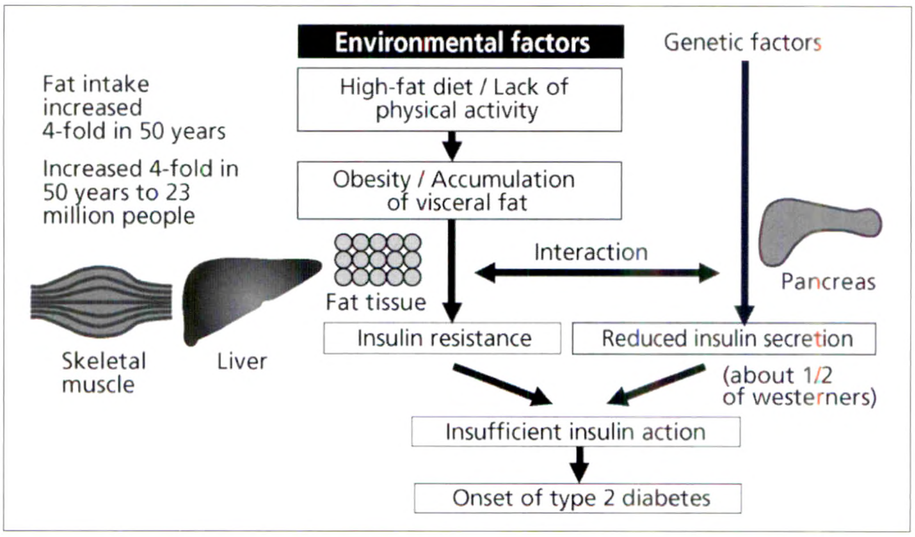

Environmental factors
Genetic factors
Fat intake increased 4-fold in 50 years
Increased 4-fold in 50 years to 23 million people
High-fat diet / Lack of physical activity
Obesity / Accumulation of visceral fat
Interaction
Pancreas
Fat tissue
Skeletal muscle
Liver
Insulin resistance
Reduced insulin secretion
(about 1/2 of westerners)
Insufficient insulin action
Onset of type 2 diabetes

**Fig. 1** Proposed mechanisms of the T2DM epidemic in Japan.

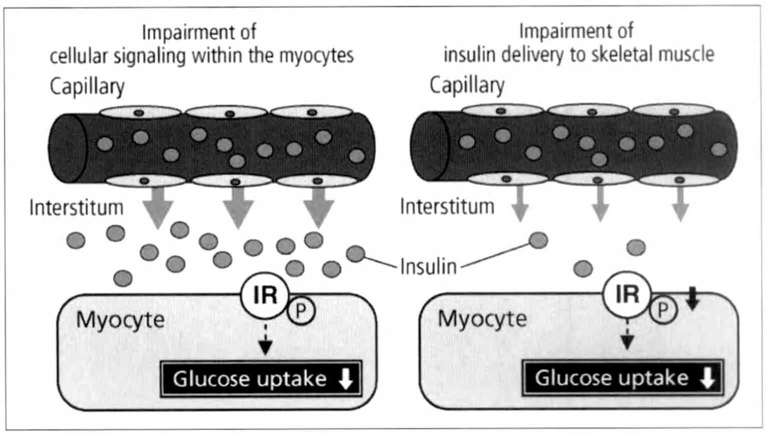


**Fig. 2** Two models of skeletal muscle insulin resistance.

concentrations of insulin was also significantly impaired in the ETIrs2KO mice from 60 min onward after insulin infusion. ETIrs2KO mice also had glucose intolerance relative to controls.[7)]

Overall, the series of experiments demonstrated that IRS-2 deletion in the endothelial cells causes an insulin signaling defect that results in impairment of insulin-induced eNOS phosphorylation, capillary recruitment, and an increase of the interstitial concentrations of insulin, resulting in the impairment of skeletal muscle glucose uptake.[7)]

*Rescue of Skeletal Muscle Insulin Resistance*

Therefore, can restoration of the insulin-induced eNOS phosphorylation rescue skeletal muscle insulin resistance in the ETIrs2KO mice?

Treatment of ETIrs2KO mice with beraprost not only increased eNOS protein levels in endothelial cells but also completely normalized capillary recruitment, interstitial insulin concentrations, and whole-body insulin sensitivity. As shown in **Fig. 3a**, expression levels of eNOS mRNA and protein were significantly increased in $PGI_2$ analog-treated ETIrs2KO mice. This effect restored the insulin-stimulated phosphorylation of eNOS. **Figure 3b** shows the restoration of insulin-induced increase of capillary recruitment by beraprost. Beraprost had no effect in eNOS knockout mice, suggesting that beraprost was eNOS dependent. Glucose uptake by skeletal muscle after insulin infusion was completely restored in beraprost-treated ETIrs2KO mice, and phosphorylation levels of Irb, as well as those of IRS-1 and Akt, in skeletal muscle induced by insulin were also completely restored by beraprost.[7)]

> "***These experiments show that insulin signaling through IRS-2 in endothelial cells is important for insulin delivery to skeletal muscle interstitium and insulinstimulated glucose uptake in muscle.***" Rask-Madsen & King (2011)[8)]

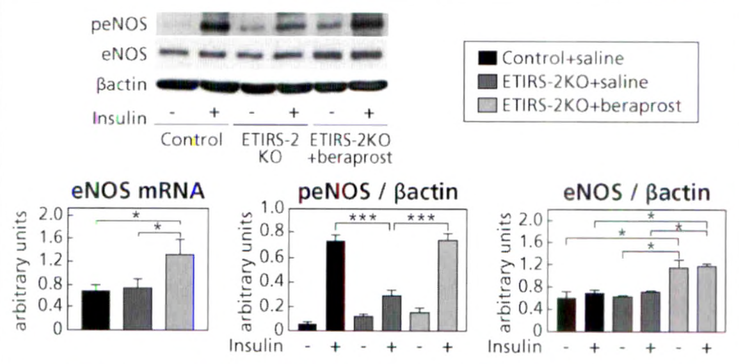
*Insulin Signaling in Hf Diet-Fed Mice*

Kubota et al. next studied mice with obesity-associated insulin resistance induced by high-fat diet and found that IRS-1 and IRS-2 in endothelial cells were downregulated by 50% and 80%, respectively. Furthermore, insulin-stimulated phosphorylations of Akt and eNOS were decreased by 70–80% in the endothelial cells of the HF diet obese mice. Capillary recruitment was also significantly impaired in the HF-diet obese mice from 60 min onward after insulin infusion. In addition, capillary blood volume increased 10 min after start of a euglycemic hyperinsulinemic clamp in control mice, followed by an increase in interstitial insulin concentrations after 60 min. In obese mice, however, the increase in capillary blood volume in skeletal muscle was blunted at 10 min, and interstitial insulin concentrations were decreased at 60 min. This suggests that insulin delivery from the blood to the interstitial space was delayed in obesity-associated insulin resistance.[7)]

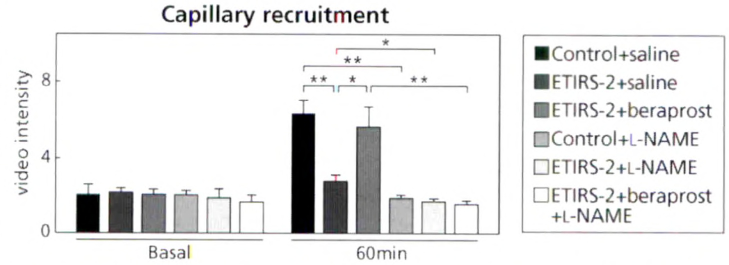
*Rescue of Skeletal Muscle Insulin Resistance in the Hf Diet-Fed Mice*

Similar to the findings in the knockout mice, and via the same proposed mechanism, treatment of HF diet-fed mice with beraprost significantly increased expression levels of eNOS mRNA and restored the insulin-stimulated phosphorylation of eNOS. Beraprost also completely restored capillary recruitment and interstitial insulin levels from 60 min onward after insulin infusion. Beraprost significantly, but not completely, restored whole-body insulin sensitivity. On the other hand, the glucose uptake by isolated skeletal muscle from the HF diet-fed mice treated with beraprost remained essentially unchanged, indicating the glucose absence of any significant effect of beraprost treatment on the glucose uptake by the skeletal muscle per se. Phosphorylation levels of Irb, as well as those of Irs1 and Akt, in skeletal muscle induced by insulin were significantly, but not completely, restored in PGI2 analog-treated HF diet obese mice.[7)]

> "***Discoveries in this field may provide targets for augmenting endothelial insulin sensitivity which may not only improve muscle insulin sensitivity but also help prevent long-term complications like atherosclerosis in people with the metabolic syndrome or diabetes.***" Rask-Madsen & King (2011)[8)]



a. Significant increase in eNOS mRNA expression following beraprost treatment of ETIRS-2KO mice
p:*<0.05, ***<0.001



b. Restoration of insulin-induced increase of capillary recruitment by beraprost treatment in ETIRS-2KO mice was completely blocked by the NOS inhibitor $N^G$-nitro-L-arginine methyl ester (L-NAME)
p:*<0.05, **<0.01

**Fig. 3** Rescue effects of beraprost in ETIrs2KO mice.[11]

*The Potential Role of Beraprost Sodium in T2 dm*

Beraprost sodium is the first chemically stable and orally active prostacyclin analog synthesized in Japan. In clinical studies, beraprost has been shown to improve PAD with ischaemic ulceration, pain at rest or peripheral coldness and to effectively treat primary pulmonary hypertension.[9–11]

Medical therapies for PAD aim to improve ischaemic symptoms, to improve patency for vascular reconstruction (including endovascular treatment) and to prevent systemic vascular events. Beraprost is one of the most commonly used of the many drugs currently available in Japan for the treatment of PAD.[12]

*Clinical Implications and Future Perspectives*

Based on the insights into the mechanism of insulin resistance in skeletal muscle provided by Kubota and colleagues, it is anticipated that, by improving insulin resistance via increased insulin delivery, beraprost sodium may prove to be a valuable therapeutic option in the overall management of T2DM. Further discoveries in the field of insulin signaling in obesity and T2DM may provide targets for augmenting endothelial insulin sensitivity to help prevent long-term complications such as atherosclerosis in people with metabolic syndrome or diabetes.

"… ***treatment directed at improving insulin signaling in the endothelial cells as well as myocytes may serve as a therapeutic strategy for ameliorating skeletal muscle insulin resistance.***" Kubota et al. (2011)[7]

With this discovery, agents that improve insulin-induced eNOS activity, such as beraprost, may serve as a new therapeutic strategy with a different mechanism of action (targeting endothelial cells) from the existing insulin sensitizers[7]:

- IRS-2 expression level was significantly decreased in endothelial cells of high-fat diet obese mice;
- eNOS activity (phosphorylation) in endothelial cells was significantly reduced in high-fat diet obese mice;
- Beraprost significantly restored the decreased eNOS activity (phosphorylation) in endothelial cells of high-fat diet-fed mice;
- Beraprost significantly improved the reduced glucose uptake of skeletal muscle.

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## Foot Care and the Prevention of Diabetic Foot

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(Seoul, Korea)

The definition of diabetic foot according to the International Consensus on the Management and Prevention of the Diabetic Foot, 2007 is infection, ulceration or destruction of deep tissues of the foot associated with neuropathy and/or peripheral arterial disease in the lower extremity of people with diabetes.

Statistics for diabetic foot show that 15% of diabetic patients will develop foot ulcers. Every year, approximately 4 million people develop a new diabetic foot ulcer; and 14–24% of people will require amputation. Up to 70% of all lower-limb amputations are performed on people with diabetes with 85% of all amputations preceded by foot ulcers. There is a 2–4 fold increase in ulcers and amputations with age and duration of diabetes.[1)]

***"Every 30 seconds, a lower limb or a part of a lower limb is lost somewhere in the world as a consequence of diabetes."***
Boulton et al. (2005)[2)]

Outlined in **Table 1** are the major risk factors for foot ulceration in diabetic patients. The most significant of these are smoking, obesity, alcohol consumption and tight footwear.

Education of diabetic patients in the prevention of diabetic foot is critical to preventing this debilitating condition. Daily feet inspection by the patient is important, including areas between the toes (frequently missed area). Should the patient be unable to do so (vision impaired), this should be done by another person with skills to inspect feet (**Fig. 1**).

In addition to daily inspection, regular washing of feet with water temperature below 37 °C followed by careful drying, especially between the toes is essential. Patients must not use a heater or hot water bottle to warm their feet. The use of lubricating oils or creams for dry skin; but not between the toes is recommended.

Patients are also advised to avoid barefoot walking indoors or outdoors, they should cut nails straight across. Chemical agents or plasters to remove corns and calluses – should not be used; these should be dealt with by a healthcare provider (**Fig. 2**).

The wearing of stocking with seams inside out or preferably without any seams is recommended and patients must never wear tight or knee-high socks. It is advised to change socks daily and most importantly, diabetic patients must never wear tight shoes.

There are four categories of risk for diabetic foot as outlined in **Table 2.** If a patient falls within category 0 they should be instructed in basic foot care. Patients in category 1 should conduct daily foot self-examination, receive diabetic foot patient education, and use in-depth shoes or sneakers with non-molded soft inlays. Category 2 requires daily foot self-examination, diabetic foot patient education, in-depth shoes or sneakers and custom-molded foot orthoses. For the most severely affected patients, category 3, daily foot self-examination; patient-at-risk diabetic foot education and the use of custom-molded foot orthoses and prescription shoes are often required.

*General Principles of Footwear Prescription*

Shoe should match the shape of the foot. They should be roomy and in-depth shoes, 1/2 to 5/8 inch longer than the longest toe, have triple depth-inlay. To minimize shear/friction shoes should have a high instep, non-leather insole.

Shoes are recommended to have heel heights less than 2 inches. Rigid rocker or roller sole are advantageous. Shoes should be fitted at the end of the day and it is advised that patients change shoes at midday and again in the evening. The role of therapeutic footwear in diabetic patients is prevention of initial or recurrent ulceration rather than healing of existing ulcers.

*In-Depth Shoes*

The Blucher-style Oxford or athletic shoe is available with an additional 1/4 to 1/2 inch of depth throughout the shoe designed to provide the extra volume needed to accommodate both the foot and a total contact orthosis. These shoes have light-weight, shock-absorbing soles, strong counters with upper materials made of soft, seam-free full leather linings with a firmer upper material of deer skin or cowhide. Charcot foot shaped wider in the midfoot area to accommodate deformity.

**Table 1. The risk factors for foot ulceration in diabetic patients**

| Risk Factors for Foot Ulceration |
|---|
| Bony abnormality – claw toes, prominent MTH |
| Soft tissue problems |
| Smoking |
| Poor vision |
| Obesity |
| Poor glycaemic control |
| Cognitive problems |
| Alcohol consumption |
| Tight footwear |
| Peripheral oedema |

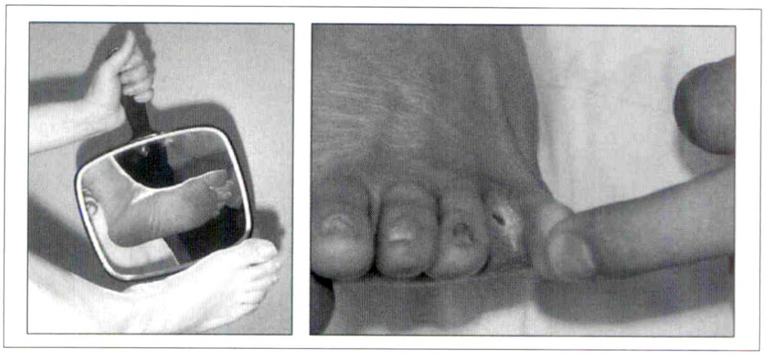

Fig. 1

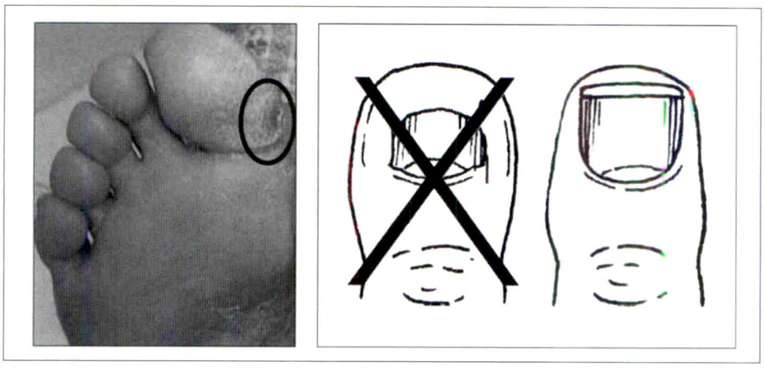

Fig. 2

Table 2. **Risk categorization – pedorthic aspect in diabetic foot**

| Category | Loss of protective sensation | Deformity, callus, weakness | History of ulceration or ischaemia | Follow-up |
|---|---|---|---|---|
| 0 | No | No | No | Annually |
| 1 | Yes | No | No | 6 Months |
| 2 | Yes | Yes | No | 3–4 Months |
| 3 | Yes | Yes | Yes | 1–2 Months |

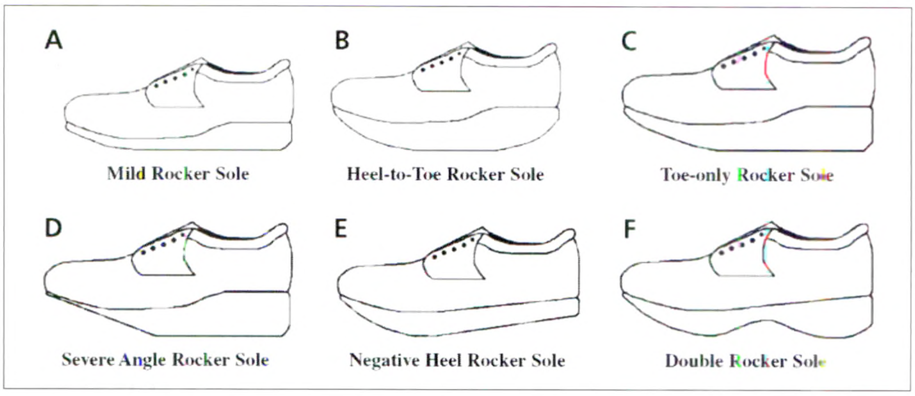

Fig. 3

*Inserts*

The use of shoe inserts is to redistribute plantar forces; pressure beneath one part of the foot can be relieved by increasing the pressure on an adjacent part. The insole design is comprised of lamination of different materials to form a single firm material. The shoe then has softer components next to the skin and firmer materials underneath for structural support.

*Midstance and Apex of Rocker Sole*

A midstance rocker sole has contact with the floor when in a standing position. An apex is located at the distal end of the midstance this must be placed behind any area for which pressure relief is desired, reducing MTH pressure by 55–60% and reducing toe pressure by 65%.

There are six types of mid rocker sole for the prevention of diabetic foot:

A. Mild: the most widely used, relieve mild metatarsal pressure, assist in gait

B. Heel-to-Toe: ankle or subtalar joint fusion, fixed claw or hammer toe deformity

C. Toe-only: forefoot ulcerations with stability or proprioception problems

D. Severe Angle: extreme relief of MTH or toe-tip ulcerations

E. Negative Heel: accommodate a foot fixed in dorsiflexion, relieve forefoot pr.

F. Double Rocker: midfoot pathology

To conclude, clinicians need to provide continuous and repetitive foot-related educations about diabetic foot. This education needs to stress the importance of frequent inspection, washing, drying, and using of oils or creams. In addition, patients need to be advised on the correct treatment of nail cutting, corns and calluses and the use of proper socks. Patients should be prescribed with proper shoes.[3–5]

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# Discussion

The discussion that followed the presentations covered several important issues, including the timing of pharmacotherapy initiation to limit the consequences of PAD in diabetic patients. Dr Nishibe usually starts treatment when PAD is diagnosed in such patients. However, if the patient has no symptoms, this can be quite difficult and in which case treatment with just aspirin is advisable. If the patient is symptomatic, then the options include cilostazol and beraprost amongst others. Dr Maeda also commented on the initiation of pharmacotherapy in diabetes patients with PAD. In his studies, beraprost sodium has been shown to have significant clinical efficacy in the treatment of PAD. Dr Maeda currently reserves cilostazol for the rather severe cases of PAD and other drugs for the more mild cases; for early treatment he would select beraprost.

A further issue addressed why the current TASC II guidelines recommends only the use of cilostazol while ample evidence is available supporting the use of beraprost and ticlopidine. Therefore, why did TASC II not consider this evidence in formulating their latest guidelines? Dr Nishibe pointed out that when the TASC II process was undertaken, its stated aim was to provide an international consensus on the diagnosis and treatment of PAD. The only drugs available worldwide at that time were aspirin, cilostazol and clopidogrel, so they were the only agents that were considered. However, Dr Nishibe believes that both beraprost and ticlopidine should be recommended for PAD patients. To keep abreast of the changing clinical landscape, the TASC II documentation is constantly evolving to encompass the latest clinical and technical updates in PAD. The guidelines, provide health care workers with the only international consensus that provides dynamic information on the diagnosis and treatment of PAD. It is hoped that subsequent guidelines take into account the compelling evidence for beraprost in the management of PAD.

The Chairman closed a highly successful third Asia PAD workshop and thanked the esteemed faculty for providing a highly stimulating and educational program. Thanks were also extended to the many delegates who had travelled from across Asia to gain invaluable insights into the epidemiology and pharmacotherapy of PAD, in addition to optimal foot care management to prevent diabetic foot complications. Importantly, recent data were also presented regarding the potential of beraprost as a new therapeutic strategy to ameliorate skeletal muscle insulin resistance in diabetes.

astellas

ASOなど慢性動脈閉塞症に伴う

# 冷感、疼痛、潰瘍の改善に。

豊かにそしてしなやかに。

**血管内皮細胞と$PGI_2$**

**【禁忌（次の患者には投与しないこと）】**
**（1）出血している患者（血友病、毛細血管脆弱症、上部消化管出血、尿路出血、喀血、眼底出血等）**
**（2）妊婦又は妊娠している可能性のある婦人**

**【効能・効果】**
○慢性動脈閉塞症に伴う潰瘍、疼痛及び冷感の改善
○原発性肺高血圧症

**＜効能・効果に関連する使用上の注意＞ 原発性肺高血圧症**
（1）原発性肺高血圧症と診断された患者にのみ使用すること。
（2）本剤は経口投与であるため、重症度の高い患者等では効果が得られにくい場合がある。循環動態あるいは臨床症状の改善が見られない場合は、注射剤や他の治療に切り替えるなど適切な処置を行うこと。

**【用法・用量】**
○**慢性動脈閉塞症に伴う潰瘍、疼痛及び冷感の改善**　通常、成人には、ベラプロストナトリウムとして1日120μgを3回に分けて食後に経口投与する。
○**原発性肺高血圧症**　通常、成人には、ベラプロストナトリウムとして1日60μgを3回に分けて食後に経口投与することから開始し、症状（副作用）を十分観察しながら漸次増量する。増量する場合には、投与回数を1日3～4回とし、最高用量を1日180μgとする。

**＜用法・用量に関連する使用上の注意＞ 原発性肺高血圧症**
原発性肺高血圧症は薬物療法に対する忍容性が患者によって異なることが知られており、本剤の投与にあたっては、投与を少量より開始し、増量する場合は患者の状態を十分に観察しながら行うこと。

**【使用上の注意】（抜粋）**
**1.慎重投与（次の患者には慎重に投与すること）**　（1）抗凝血剤、抗血小板剤、血栓溶解剤を投与中の患者（「相互作用」の項参照）（2）月経期間中の患者［出血傾向を助長するおそれがある。］（3）出血傾向並びにその素因のある患者［出血傾向を助長するおそれがある。］
**2.重要な基本的注意**　（1）本剤の有効成分は「ケアロードLA錠60μg」、「ベラサスLA錠60μg」と同一であるが、原発性肺高血圧症において用法・用量が異なることに注意すること。（2）原発性肺高血圧症において「ケアロードLA錠60μg」、「ベラサスLA錠60μg」から本剤へ切り替える場合には、「ケアロードLA錠60μg」、「ベラサスLA錠60μg」の最終投与時から12時間以上が経過した後に、本剤をベラプロストナトリウムとして原則1日60μgを3回に分けて食後に経口投与することから開始すること。また、「ケアロードLA錠60μg」、「ベラサスLA錠60μg」と同用量の本剤に切り替えると、過量投与になるおそれがあるため注意すること。
**3.相互作用　併用注意（併用に注意すること）**　抗凝血剤（ワルファリン等）、抗血小板剤（アスピリン、チクロピジン等）、血栓溶解剤（ウロキナーゼ等）、プロスタグランジン$I_2$製剤（エポプロステノール、ベラプロスト注1)）、エンドセリン受容体拮抗剤（ボセンタン）注1）同一有効成分を含有する「ケアロードLA錠60μg」、「ベラサスLA錠60μg」等との併用に注意すること。
**4.副作用**　○**慢性動脈閉塞症に伴う潰瘍、疼痛及び冷感の改善**　総症例7,515例中、370例（4.9%）に副作用（臨床検査値異常を含む）が認められ、その主なものは頭痛91例（1.2%）、顔面潮紅60例（0.8%）、ほてり39例（0.5%）、下痢29例（0.4%）、嘔気20例（0.3%）等であった。（再審査結果通知：1999年3月）
○**原発性肺高血圧症**　肺高血圧症の臨床試験において総症例40例中、24例（60.0%）に副作用（臨床検査値異常を含む）が認められ、その主なものは頭痛9例（22.5%）、LDH上昇5例（12.5%）、ビリルビン上昇4例（10.0%）、ほてり3例（7.5%）、下痢3例（7.5%）、嘔気3例（7.5%）、トリグリセライド上昇3例（7.5%）等であった。（効能追加時：1999年9月）
使用成績調査において総症例244例中、57例（23.4%）に副作用（臨床検査値異常を含む）が認められ、その主なものは頭痛15例（6.1%）、AST（GOT）上昇9例（3.7%）、ALT（GPT）上昇8例（3.3%）、ほてり8例（3.3%）、顔面潮紅4例（1.6%）、倦怠感4例（1.6%）等であった。このうち、小児（15歳未満）については66例中、14例（21.2%）に副作用（臨床検査値異常を含む）が認められ、その主なものは鼻出血3例（4.5%）、AST（GOT）上昇3例（4.5%）、ALT（GPT）上昇3例（4.5%）、頭痛2例（3.0%）、ほてり2例（3.0%）等であった。（再審査申請時）
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The first issue of the Annals of Vascular Diseases was published in Japan, in 2007.

The Journal publishes peer-reviewed original research articles, editorials, reviews, and case reports in vascular research, vascular medicine, surgery, and allied fields. To aid in the development of the growing field of vascular medicine in Asia, the Japanese College of Angiology, the Japanese Society for Vascular Surgery and the Japanese Society of Phlebology collaborated to sponsor this new journal. Since October 2008, AVD is the official journal of Asian Society for Vascular Surgery, and since June 2010, the official journal of the Asian Venous Forum.

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**Review Article**

# Recent Advances in Medical Treatment for Lymphedema

Yoshihiro Ogawa, MD

**As medical treatment for lymphedema, combined physical therapy with guidance regarding daily living is recommended. Recently, training has been conducted on a nationwide scale, and this therapy has gradually and commonly been employed. This therapy consists of daily living guidance to prevent edema deterioration, skin care, manual lymph drainage, compression therapy, and exercise therapy. The number of hospitals in which all procedures can be adequately performed is limited. There is no treatment to completely cure lymphedema. Patients' self-care based on the contents of treatment is essential for relieving symptoms. (*English Translation of J Jpn Col Angiol 2008; 48: 167-172.)**

***Keywords:*** lymphedema, medical treatment, combined physical therapy, intermittent pneumatic compression

## INTRODUCTION

It is difficult to completely cure lymphedema. Chronic conditions are more difficult to reduce. As both health care professionals and patients often abandon positive treatment, the absence of care leads to a severer condition in some patients. However, appropriate medical treatment early after the onset of lymphedema and guidance for patients' self-care may prevent the deterioration of lymphedema, as demonstrated for diet/exercise therapies in patients with lifestyle-related diseases such as diabetes. To instruct patients with lymphedema, health care professionals must acquire knowledge regarding lymphedema treatment. However, currently, few physicians are familiar with the pathogenesis and treatment of lymphedema.

Primary treatment recommended by the International Society of Lymphology[1)] is presented in **Table 1**. Concerning surgery, with the recent, widespread application of microscopic lymph vessel-vein anastomosis, its efficacy has been reported. However, there is no recently advanced effective medical treatment technique. For medical treatment, combined physical therapy (CPT) is primarily performed. Internationally, it is employed as standard treatment. However, it has not commonly been selected in Japan; considering this, CPT may be the latest treatment in Japan. At the Lymphedema Training Committee of the "Cancer Rehabilitation Training" program organized by the Ministry of Health, Labour and Welfare in 2009, "complex treatment (conservative treatment involving CPT)" consisting of CPT and guidance regarding daily living was established as standard treatment for lymphedema.

In this article, we introduce the entity of lymphedema treatment, as well as medical treatment with CPT. We also review therapies described in the literature.

## ENTITY OF LYMPHEDEMA TREATMENT

Lymphedema is classified into two types: primary lymphedema associated with congenital lymph vessel dysplasia/dysfunction in the absence of etiological factors, and secondary lymphedema resulting from lymph vessel injury related to surgery with lymph node dissection or radiotherapy/chemotherapy for malignant disorders. Regardless of these types, peripheral lymph is not transported from sites with lymph vessel hypo-function, leading to lymphedema through the subcutaneous tissue retention of inter-tissue fluid. Lymphedema is characterized by such edema involving subcutaneous tissue.

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**Table 1 Treatment of lymphedema**

| Non-operative Treatment | Operative Treatment |
|---|---|
| 1. Physical therapy<br>a.Combined physical therapy(CPT)<br>b.Intermittent pneumatic compression<br>c.Massage alone<br>d.Wringing out<br>e.Thermal therapy<br>f.Elevation | 1. Microsurgical procedures<br>a.Reconstructive methods<br>b.Derivative methods<br>2. Liposuction<br>3. Surgical resection |
| 2. Drug therapy<br>a.Diuretics<br>b.Benzopyrones<br>c.Antimicrobials<br>d.Filariasis<br>e.Mesotherapy<br>f.Immunological therapy<br>g.Diet | |
| 3. Psychosocial rehabilitation | |

**Table 2 CPT**

1. Skin care
2. Manual lymph drainage (MLD)
3. Compression by multi-layered bandage-wrapping or compression garments
4. Exercise

CPT: combined physical therapy

Thus, for lymphedema treatment, it is necessary to promote the development of a collateral pathway from the affected toward the normal lymphatic system, decrease leakage from capillaries to inter-tissue spaces, and inhibit the gravity-related transfer of inter-tissue fluid to the periphery of an affected limb. In particular, it is important to control the subcutaneous tissue of an affected limb. Furthermore, prolonged edema may induce subcutaneous-tissue fibrosis or adipose-tissue outgrowth.[2] Therefore, treatment should be started early after onset, when tissue changes are slight.

## CPT

In the lymphedema-associated literature, CPT is described as complex/complete decongestive therapy (CDT) or complex decongestive physiotherapy (CDP). Many studies have reported its efficacy.[3-10] Furthermore, the number of reports on its efficacy in Japan has slightly increased. In Europe and the United States, there are several hospitals with beds in which CPT is performed. However, in Japan, CPT is not covered by health insurance. In addition, there are few hospitals to which patients can be admitted.

The purpose of this treatment is to eliminate lymph and inter-tissue fluid retention in an affected limb through skin care, manual lymph drainage (MLD), compression therapy, and exercise therapy under compression, as shown in **Table 2.** The detailed contents of individual therapies are described in other articles. In this article, we introduce basic constitutive matters and their outlines.

### (1) Skin care

For lymphedema treatment, it is most important to avoid the onset/deterioration of edema in patients' daily lives. Excessive exercise and travelling may cause edema. However, lymphedema rapidly deteriorates after inflammation such as cellulitis. In affected limbs, the lymph vessel function is damaged, and bacterial infection may become severer. Inflammation enhances capillary permeability, leading to the deterioration of edema.

To prevent affected-limb infection, it is important to avoid skin injury and clean the skin. When edema of the fingers or toes is present, inter-finger/-toe wetness may induce trichophytia. Caution is needed.

### (2) MLD

In this procedure, inter-tissue fluid and lymph retaining in the subcutaneous tissue of an affected limb are slowly induced to the normally functioning lymphatic system with soft stimuli. Treatment is focused on the subcutaneous tissue of an affected limb. "Soft compression" transmitting from the skin surface to the entire subcutaneous tissue is appropriate. Strong forces such as digital compression and massage are not necessary.

Lymph should always be induced from the affected limb toward normal lymph nodes. The detailed procedures are described in another article.11) However, it is important to treat affected limbs involving the trunk. Before affected-limb treatment, deep lymphatic flow should be promoted, and the trunk involving the central end of the affected limb must be massaged. Sites of marked fibrosis or sclerosis are sometimes more strongly massaged compared to other areas.

A study indicated the efficacy of simple lymphatic drainage,12) which refers to guidance-based self-MLD. In our hospital, patients are also instructed to perform CPT as self-care. However, its effects are insufficient in some patients due to their ages and natures.

### (3) Compression therapy

For CPT, compression therapy is the most important. Even when MLD is thoroughly performed, edema does not reduce in the absence of compression. In contrast, when compression is adequately carried out despite insufficient MLD, edema reduces. Inadequate compression in the topical area of the affected limb may deteriorate edema, although compression therapy is important. Caution is needed.

The reasons for affected-limb compression include the inhibition of leakage from capillaries through an increase in the subcutaneous tissue pressure, prevention of lymph regurgitation from an injured lymph vessel to subcutaneous tissue, prevention of gravity-related tissue fluid transfer, and improvement of venous return.

For compression therapy, elastic garments (elastic stockings/sleeves/gloves) and bandages are employed. Individual tools are selected in accordance with the condition.13) In patients with dermal sclerosis in the chronic phase and those with marked articular ring constrictions related to a severe status, adequate elastic garments must be introduced after treatment with elastic bandages. When only elastic garments are employed, excessive compression in the articular region may promote dermal sclerosis in some cases; improvement in edema may not be achieved.

Compression with elastic bandages should be performed at an appropriate pressure so that daily activities are not restricted. In addition, the periphery of the affected limb should be rolled with a bandage at a maximum pressure so that the bandage gradually loosens toward the central side.

Compression with elastic garments is essential for maintaining lymphedema-reducing effects. The size of elastic garments should be determined in accordance with the affected limb's circumference. The pressure must also be established (standards: ankle, 30 mmHg; and wrist, 20 mmHg; an optimal pressure should be reviewed based on the affected limb's condition). As excessive elastic garment-related compression of the affected limb leads to the deterioration of edema, stocking-type garments are employed in many patients with edema of the lower limbs, including unilateral-limb edema. In those with upper-limb edema, sleeves with gloves are also used. The characteristics of elastic garments vary; edema improvement depends on the type of garment. Therefore, health care professionals must select elastic garments appropriate for affected limbs based on their experience.

Compression therapy is contraindicated for conditions with acute inflammation such as cellulitis, congestive heart failure, and acute-phase venous thrombosis. This therapy must also be carefully selected in patients with sensory paralysis, neuroparalysis, or occlusive peripheral artery disease (contraindicated for limbs with severe ischemia).

Concerning compression therapy with elastic bandages, it is also possible to instruct patients to perform self-care. However, this is difficult in some patients, as described for MLD.

### (4) Exercise therapy under compression14–16)

Exercise under adequate compression of the affected limb is effective for lymphedema. When the affected limb is compressed on the skin surface, muscular movement-related pumping actions are added to the subcutaneous tissue, showing massage effects through intermittent increases in the tissue pressure. Leakage from capillaries is inhibited, leading to edema improvement. Furthermore, the lymph vessel pressure improves the valve function, promoting lymph induction. However, excessive exercise may cause inflammation. It should be avoided.

Patients with edema of the lower limbs should do exercise to move each joint, such as walking. Even when walking is difficult, the ankles and knees should be flexed/extended while on a bed. In those with upper-limb edema, repeated gripping movement and flexion/extension/pronation/supination of each joint are effective.

### (5) CPT as palliative care

The progression of malignant disorders also induces edema. In some cases, CPT is also performed to relieve symptoms. In such cases, edema improvement is not achieved. However, when patients wish to reduce edema due to the edema-related reduction of activities of daily living (ADL), treatment is performed to relieve symptoms.

For CPT as a part of palliative care, affected limbs are compressed with elastic bandages more loosely in comparison with general lymphedema treatment in many patients after evaluating the general condition, such as the progression of cancer and presence or absence of pleural effusion/ascites. For MLD, low-level stimuli should be given under a weak pressure in a short duration. This must be conducted in accordance with patients' conditions. In particular, skin contact on MLD exhibits supportive effects including mental actions; this procedure is useful for palliative care. It must be considered that excessive elastic garment-related compression deteriorates cancerous pain.

## OTHER MEDICAL TREATMENTS

We introduce other treatments presented in **Table 1**. However, there are only a few high-evidence-level reports.

### (1) Elevation

Simple elevation of the affected limb reduces swelling in some patients with initial-phase lymphedema. However, edema deteriorates during the daytime, when the affected limb is suspended. Therefore, elastic garment-reduced conditions should be maintained.

### (2) Intermittent pneumatic compression[17–19]

In this procedure, a cuff is worn on the affected limb, and air is intermittently infused from the periphery of the affected limb toward the center for compression. Its therapeutic effects remain controversial. However, treatment with this system is performed in most hospitals in which CPT has not been introduced to treat lymphedema. The limitation of this system is the order of compression. Edematous fluid at the periphery is transported to the central region of the affected limb, which may deteriorate edema in the central region. Therefore, MLD must be additionally conducted in the central region of the affected limb and trunk before and after this procedure. Furthermore, strong compression for a long duration should be avoided, considering the risk of lymph vessel injury.

This procedure does not replace MLD, and should be recognized as an MLD-assisting method. Health care professionals must understand this. Furthermore, compression with elastic garments/bandages after the use of this system is essential.

### (3) Massage therapy

This therapy refers to massage as single therapy. Few studies have examined the effects of classical massage or rubbing. Their effects may be limited because the affected limb is not compressed, differing from CPT. Excessive partial compression may damage lymph vessels. This is contraindicated.

### (4) Diet therapy

Factors deteriorating lymphedema include obesity. It is important to maintain an "optimal body weight." In our hospital, body weight control reduced lymphedema in some obese patients, whereas marked obesity deteriorated lymphedema in others. Although there is no specific diet therapy, the combination of "caloric restriction" and a "guidance-based exercise program" for obese patients in combination with CPT is more useful for reducing swelling of the affected limb. Furthermore, excessive salt/water ingestion should be avoided, as indicated for other types of edema.

### (5) Drug therapy

① Diuretics: Diuretics promote the excretion of whole-body water as urine. Therefore, in the initial phase, these agents are effective in some patients. However, lymphedema treatment is limited, and these agents may induce body-fluid/electrolyte imbalance. Long-term administration should be avoided.

② Benzopyrones: Oral benzopyrones may hydrolyze tissue protein while activating the lymph transport route, promoting its absorption. In Japan, a melilous extract (Esberiven) has been employed, but is not commercially available. However, this agent does not replace CPT. A long interval is required until the appearance of its effects. Long-term or massive therapy may cause hepatopathy.

③ Antimicrobial agents: Antibiotics are employed to treat acute infectious inflammation of affected limbs. Inflammation is characterized by flare, swelling, pain, fever, and septic shock, which is rare. After confirming hematological findings of inflammation, such as leukocytosis and positive reactions to C-reactive protein (CRP), broad-spectrum antibiotics, including penicillins and cephems, should be administered, and CPT must be discontinued for resting. Antibiotic therapy should be discontinued based on hematological data to avoid incomplete treatment or excessive administration.

④ Traditional Chinese herbal medicines: Various traditional Chinese herbal medicines are employed. However, these agents may not exhibit any marked effects.

### (6) Immunotherapy

For auto-lymphocyte arterial injection therapy, autologous lymph activated and infused into arteries may activate macrophages in the affected-limb interstitial tissue, decomposing an excess level of protein. However, its persistent effects remain to be clarified.

### (7) Gene therapy

In patients with primary lymphedema, gene abnormalities were reported. Gene therapy has also been examined.

Recent studies reported hepatocyte growth factor (HGF)-related neovascularization. Currently, a basic study regarding lymph vessel neogenesis therapy with HGF is being conducted. Clinical studies of HGF were carried out to investigate peripheral vascular growth in limbs with severe ischemia.[20,21] HGF-related lymph vessel neogenesis in a rat breast cancer model was reported. Furthermore, the motor ability of lymph vessels was maintained. In the future, a clinical study will be conducted.

## STRATEGIES FOR THE WIDESPREAD APPLICATION OF LYMPHEDEMA TREATMENT

As marked changes in medical environments regarding lymphedema treatment in Japan, the "lymphedema guidance/management fee" and "medical benefit for elastic garments" became covered by health insurance when medical fees were revised in 2008. Since 2008, a clinical path to lymphedema treatment and leaflets for guidance have been prepared by the Anti-Cancer Global Strategy Research Business Team, Ministry of Health, Labour and Welfare, and published on the "Cancer Information Service" homepage. Since 2009, training for "lymphedema guidance" with cancer rehabilitation, as described above, has been performed so that the instructors' level meets the widespread application of CPT for lymphedema. In the future, an authorization/qualification system for health care professionals engaged in lymphedema treatment will be established.

## CONCLUSION

As lymphedema is associated with irreversible changes in the lymphatic system, it is difficult to develop radical treatment. In particular, it is more difficult in chronic-phase patients with dermal sclerosis and an increase in the volume of fibrous and adipose tissues. Recent advances in medical treatment are not marked. Conventional CPT is still primarily selected. However, recently, education of health care professionals responsible for treatment early after onset and self-care guidance for patients have been emphasized. In Japan, CPT has not yet been applied on a nationwide scale. There is no system for all lymphedema patients to undergo sufficient treatment. However, in the future, a system for lymphedema patients to similarly receive guidance/treatment throughout Japan should be established, as introduced for guidance regarding diet/exercise therapies for lifestyle-related diseases.

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**Review Article**

# Recent Developments in Morphology of Lymphatic Vessels and Lymph Nodes

Osamu Ohtani, MD, PhD, and Yuko Ohtani, MD, PhD

**This paper reviews the morphology of lymphatics and lymphangiogenesis in vivo, microenvironments that promote lymphangiogenesis, and the structure and function of lymph nodes. Lymphatic capillaries consist of a single layer of lymphatic endothelial cells (LECs) and have valves, while collecting lymphatics are endowed with smooth muscle cells (SMCs) and valves besides a single layer of LECs. In the embryonic rat diaphragm, LECs first migrate presumably according to interstitial fluid flow and later join to form lymphatic vessels. SMCs of the collecting lymphatics are apparently differentiated from mesenchymal cells. LECs cultured on Cell Culture Inserts under a low oxygen condition proliferate very well and form a lymphatic network. LECs cultured on a collagen fiber network with a natural three-dimensional (3D) architecture under low oxygen rapidly form a 3D lymphatic network. The lymph node initiates an immune response as a critical crossroads for the encounter between antigen-presenting cells, antigens from lymph, and lymphocytes recruited into nodes from the blood. The node consists of spaces lined with LECs and parenchyma. High endothelial venules in the node strongly express Aquaporin-1, suggesting their involvement in the net absorption of water from lymph coming through afferent lymphatics. SMCs in node capsules seem to be involved in squeezing out lymphocytes and lymph. (*English Translation of J Jpn Col Angiol 2008; 48: 107-112.)**

***Keywords:*** lymphatic vessel, lymphangiogenesis, lymph node, metastasis, lymphedema

## INTRODUCTION

The lymphatic vessels maintain the homeostasis of tissue fluid, function as an immunological surveillance mechanism in the living body, and play an important role in ingesting fat and the fat-soluble vitamins A, D, E, and K. The lymphatic vessels were first identified by an Italian anatomist, Gasparo Aselli, as "milky veins" in the canine mesentery in 1627. Since then, various techniques have been developed to investigate the lymphatic vessels to reveal their distribution and structure.1) However, it was often difficult to identify lymphatic vessels in a tissue section because no specific marker was available. At the end of the 20th century, lymphatic vessel-specific markers, such as Prox-1,2) podoplanin,3) LYVE-1,4) VEGFR-3,5) CCL21,6) and desmoplakin,7) were discovered. These markers have accelerated investigations on lymphatic vessels, and should advance the diagnoses and treatments of various lymphatic disorders. The lymph node is an important intersection of antigen-presenting cells, antigens carried by the lymphatic vessels, and lymphocytes supplied by the blood. The lymph node consists of a lumen surrounded by lymphatic endothelial cells and parenchyma, featuring a reticular structure filled with lymphocytes, etc. The water of lymph from the afferent lymphatic vessels is absorbed into the lymph node to

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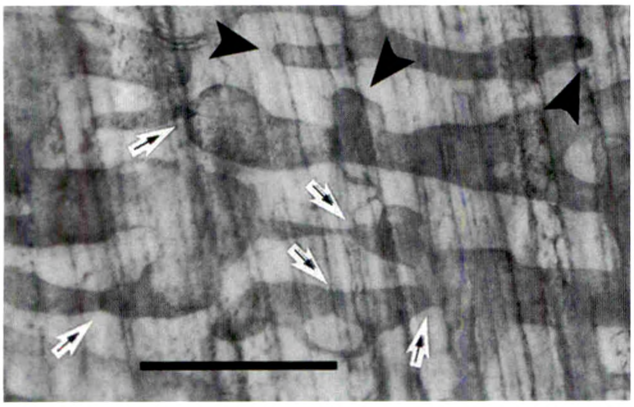

**Fig. 1** Lymphatic capillaries in the rat diaphragmatic pleura. There are many blind ends (arrowheads) and valves (arrows). Enzyme histochemistry for 5′-nucleotidase. Scale bar =200m (From Ohtani et al., 1993[18])
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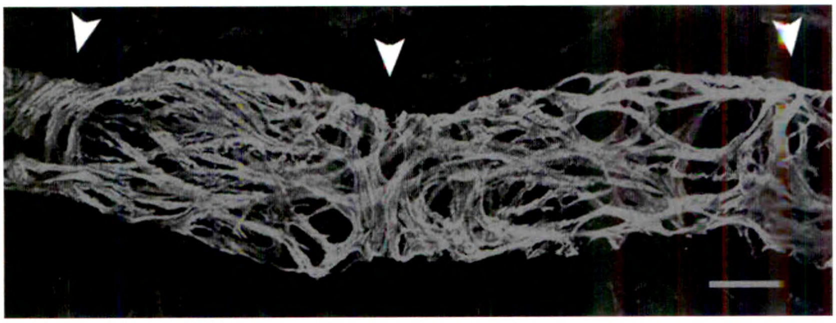

**Fig. 2** Smooth muscle cells around the collecting lymphatic vessel in the rat diaphragm. They tend to run circumferentially around the valves (arrows) and obliquely or helically between valves. Scale bar = 50m (From Ohtani et al., 2001[19])
©2001 Archives of Histology and Cytology. All rights reserved. Ohtani Y, Ohtani O: Postnatal development of lymphatic vessels and their smooth muscle cells in the rat diaphragm: a confocal microscopic study. 2001, **64**: 513-522.

concentrate proteins. Lymph node metastasis of a tumor is the main negative prognostic factor. However, lymphadenectomy for cancer treatment causes lymphedema. We herein describe the morphology, structure, and functions of lymphatic vessels and lymphangiogenesis.

## MORPHOLOGY OF LYMPHATIC VESSELS

There are two kinds of lymphatic vessel: lymphatic vessels of origin, or lymphatic capillaries and lymphatic aggregates. The lymphatic capillary consists of a layer of lymphatic endothelial cells (LECs). Most lymphatic capillaries have valves at intervals of hundreds of microns to several millimeters to allow one-directional lymphatic flow (**Fig. 1**). Unlike blood vessels, the lymphatic capillary features a poorly-developed basal membrane and no pericyte. The lymphatic vessels are bound to the surrounding extracellular matrix through an anchoring filament[8] containing fibrillin.[9] Doubly or triply overlapping adhesive regions and gating non-adhesive micro valves exist between LECs. A pressure rise in the interstitial fluid increases the tension of the anchoring filaments attached to the LECs, thereby dilating the lymphatic capillary. Then, the non-adhesive regions between LECs open to allow liquid, macromolecules, and cells to enter the lymphatic vessels.

The lymphatic aggregates have valves and smooth muscles. Smooth muscles contract to cause lymphatic transport. Smooth muscles tend to run circularly around the valves and obliquely between the valves (**Fig. 2**). The smooth muscles in the lymphatic aggregates develop depending on the regions and species.

The human thoracic duct has three layers of well-developed smooth muscles. Smooth muscles run longitudinally in the inner layer and circularly in the middle layer. The smooth muscle bundles run obliquely or spirally in the

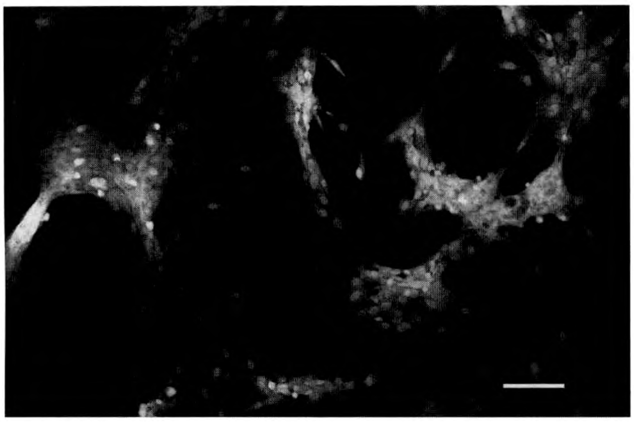

**Fig. 3** LECs expressing LYVE-1 from the thoracic duct of the green rat (transgenic SD rats containing fluorescent genes; Amersham, Tokyo) cultured on an insert under a low oxygen condition proliferate rapidly and form a lymphatic-like network. Scale bar = 100m

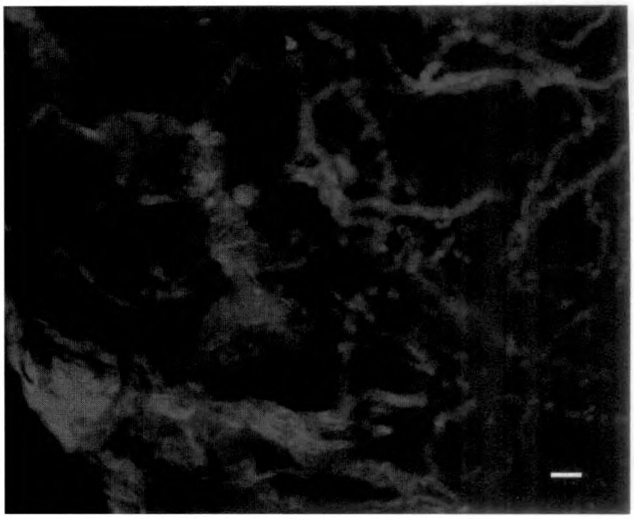

**Fig. 4** LECs from the rat thoracic duct cultured on a collagen fiber sheet from the human thoracic duct rapidly form a three-dimensional lymphatic network. Scale bar = 25m

outer layer.[10)] The middle layer is the thickest, and the inner and outer layers are relatively thinner. These layers cause peristaltic movement to allow lymphatic transport against gravity.

## LYMPHANGIOGENESIS

In 1902, Sabin (Florence) proposed that primitive lymph sacs are formed through sprouting from the veins in an early developmental stage, from which the endothelium sprouts into the surrounding tissues and organs to form peripheral lymphatic vessels.[11)] Oliver (2004) employed genetically-engineered mice to demonstrate Sabin's hypothesis that mammalian lymphatic vessels develop from embryonic veins.[12)]

VEGF-C promotes the proliferation and migration of cultured LECs through VEGFR-3.[13)] Furthermore, VEGF-A, VEGF-C, and VEGF-D promote lymphangiogenesis through VEGF receptor or neuropilin 2. The molecular regulatory mechanisms of lymphangiogenesis have been rapidly elucidated. For details, see a review.[14)]

Environmental factors that promote LEC proliferation and lymphangiogenesis remain unclear. LECs collected from the rat thoracic duct more rapidly reached confluency when cultured under hypoxic conditions than when cultured under a 5% $CO^2$ atmosphere. LECs cultured on an insert under hypoxic conditions proliferate in layers to form lymphatic vessels (**Fig. 3**). Cells collected from the human thoracic duct and diaphragm were dissolved. Only the collagen fiber network was removed, with its natural three-dimensional structure maintained.[15,16)] LECs cultured on the network under hypoxic conditions rapidly formed lymphatic vessels in three dimensions (**Fig. 4**). These findings suggest that a hypoxic environment and three-dimensional scaffold are critical for lymphangiogenesis.[17)]

Only a few studies have been conducted on the in vivo development of lymphatic vessels. We have investigated lymphatic vessel development in the rat diaphragm.[18–20)] Lymphatic vessels can be clearly recognized in the thoracic region of the diaphragm from embryonic day 16. After a while, they also appear in the peritoneal region. Lymphatic vessels develop mainly through sprouting. However, we previously suggested that LECs discretely migrated to form a line in regions where lymphatic vessels may be formed and the LECs aggregated to form lymphatic vessels (**Fig. 5**).[17)] Alternatively, the LECs discretely migrate in the direction of interstitial fluid flow and subsequently aggregate to form lymphatic vessels.[21)]

Little attention has been paid to the development of smooth muscles in lymphatic aggregates. Our study on the rat diaphragm[19)] revealed many spindle-shaped cells expressing α-smooth muscle actin (α-SMA) until two weeks after birth. Subsequently, α-SMA-positive cells wrapped with elongated extensions were observed around the lymphatic vessels. After a while, typical smooth muscles circularly or spirally bound to the lymphatic vessels were observed. These findings suggest that the smooth muscles of lymphatic vessels differentiate from mesenchymal cells.[19)]

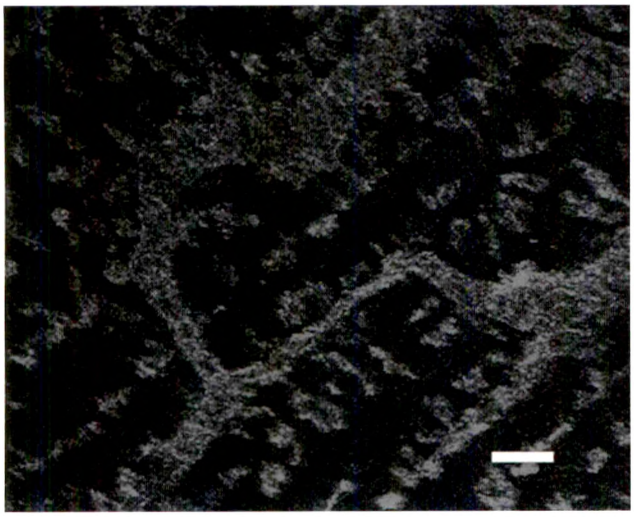

**Fig. 5** Developing lymphatic vessels in the rat diaphragm. Numerous single LECs are in lines in the places where lymphatic vessels are expected to be formed. L: lymphatic vessels already formed. Scale bar = 50m

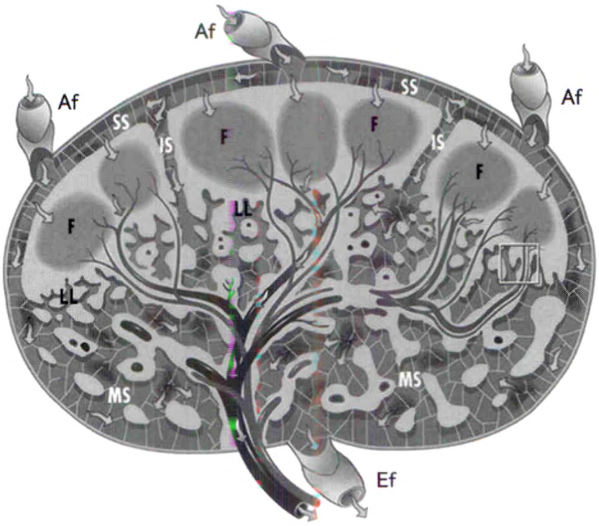

**Fig. 6** Schematic diagram of the rat lymph node showing an overview of lymphatic pathways (green), an artery (red) and veins (violet: HEVs; blue: ordinary vein) of the lymph node. Arrows indicate the direction of fluid flow. Cross lines in subcapsular sinuses (SS), intermediate sinus (IS), and medullary sinuses (MS) indicate the networks of intraluminal reticular cells (i.e., lymphatic endothelial cells). F: follicle, Af: afferent lymphatic vessels, Ef: efferent lymphatic vessels, LL: lymphatic labyrinth. (From Ohtani et al., 2003[22])

©2003 Archives of Histology and Cytology. All rights reserved.Ohtani O, Ohtani Y, Carati CJ et al: Fluid and cellular pathwaysof rat lymph nodes in relation to lymphatic labyrinths and Aquaporin-1 expression. Arch Histol Cytol, 2003, **66**: 261-272.

## Structure and Functions of Lymph Nodes

The lymph node is an important intersection of antigen-presenting cells, antigens carried by the lymphatic vessels, and lymphocytes supplied by the blood to initiate an immune response. The lymph node consists of a lumen surrounded by lymphatic endothelial cells and parenchyma, featuring a reticular structure filled with lymphocytes, etc.[22] In the parenchyma, the cortex is connected to myelin through the deep cortex. The afferent lymphatic vessels flow into the cortical lymphatic sinuses. Fluid and cells enter the cortex through the pores on the bed of the cortical lymphatic sinuses (**Fig. 6**). A lymphatic labyrinth filled with lymphocytes exists in the deep cortex. The lymphatic labyrinth is connected to the medullary sinuses. The medullary sinuses feature a large internal diameter with a well-developed beam column surrounded by LECs and many macrophages entangled. The cortical lymphatic sinuses are also connected to the medullary sinuses through the intermediary sinuses. The intermediary sinuses have the same structure as the medullary sinuses. High endothelial venules (HEVs) develop in the deep cortex. Circulating lymphocytes enter the lymph node parenchyma through the HEV wall (**Fig. 7**). On the other hand, lymphocytes from the parenchyma enter the lymphatic labyrinth in the deep cortex (**Fig. 7**). CCR7 is expressed in the lymphatic labyrinth.

Lymph from the afferent lymphatic vessels is absorbed into the lymph nodes to concentrate proteins.[23] This mechanism remains unclear. Water may be absorbed from the HEV wall into the blood vessels, because a water channel called Aquaporine-1 is strongly expressed near the surface of the endothelial cells of HEVs.[22] This suggests a functional intravenous shunt of lymphatic vessels in the lymph node.

Lymph node metastasis of a tumor is the main aggravating factor of patient prognosis. Recently, some kinds of human tumor were found to produce VEGF-A, -C, and -D. Such tumors facilitate lymphatic vessel proliferation and promote sentinel lymph node metastasis.[24] VEGF-C expression is correlated with Cox-2 expression in human stomach and colorectal cancers.[25,26] Reportedly, a Cox-2 inhibitor suppresses lymphangiogenesis when administered to an experimental tumor model. Thus, lymphangiogenesis inhibition in a tumor has been investigated as a cancer therapy strategy.

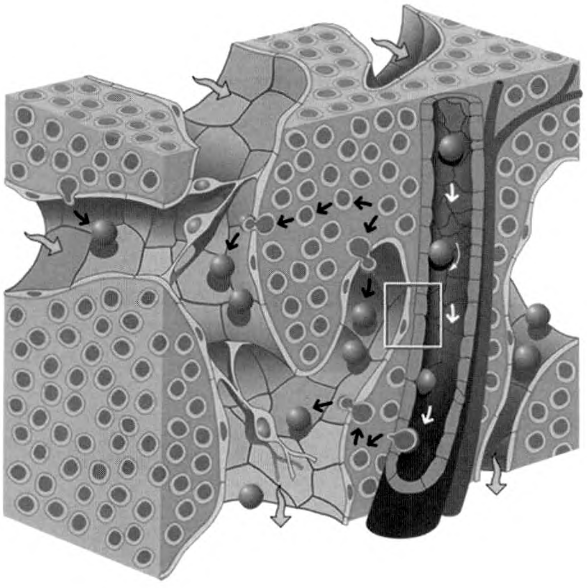

**Fig. 7** Schematic of a closer view of the boxed area in **Fig. 6**. Thicker white arrows indicate a possible time sequence for the uppermost lymphocyte flowing in a HEV, which subsequently rolls on (thinner white arrow), then adheres to the luminal surface, and finally penetrates through its endothelium to enter the lymph node parenchyma. Black arrows indicate that lymphocytes in the lymph node parenchyma move towards the lymphatic labyrinths, and penetrate through their endothelium to enter the labyrinths. Yellow arrows indicate the lymph flow direction. (From Ohtani et al., 2003[22])

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The mechanism of tumor cell metastasis to the lymph node remains unclear. Lewis lung carcinoma (LLC) cells, transplanted in the mouse lung, metastasize to the mediastinal lymph node.[27] GFP-expressing LLC cells were investigated as a model to demonstrate that LLC cells reached and scattered in the cortical lymphatic sinus and proliferated to form a tumor nodule. LLC cells scatter around the nodule and exist independently or form a small cell population. LLC cells that passed through the medullary sinus metastasize to other lymph nodes. Preventing tumor cells from passing through the medullary sinus may also provide an effective cancer therapy strategy.

Well-developed smooth muscles exist in the capsule of the lymph node. Smooth muscles in the capsule of the lymph node are better developed in the axillary or inguinal lymph nodes than in the cervical lymph nodes. Lymphocytes and lymph are squeezed out by the capsular smooth muscles into the efferent vessels. The lymph nodes absorb about half of the water in the lymph into the blood. Lymphadenectomy for cancer treatment often causes lymphedema. Lymphadenectomy abrogates the above two functions of the lymph nodes to cause lymph retention and lymphedema. Lymphatic-venous anastomosis, as well as conservative therapies, such as lymph drainage and donning of an elastic stocking, is effective in treating lymphedema. Autologous lymph node transplantation should be therapeutically effective.

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**Original Article**

# Diabetes-Related Lower Extremities Amputations in Saudi Arabia: The Magnitude of the Problem

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***Background:*** **Data on diabetes-related lower extremities amputations in the Kingdom of Saudi Arabia (KSA) and perhaps in all of Middle East and North African (MENA) countries are limited, in view of the absence of national registries.**
***Methods:*** **This review aims to challenge media figures by review of data in the local database of the author, available published data, as well as by analysis of recent annual reports of the Saudi Ministry of Health to estimate the magnitude of the problem. Different methods of analysis are used based on the number of beds, operations and admissions in KSA to generate approximate figures of the annual expected numbers of amputations in KSA and MENA countries. The 2010 International Diabetes Federation IDF comparative prevalence rate of 16.8% was used to standardize the analysis methods.**
***Results:*** **Findings of 2 previous studies and 3 analytical methods led me to the prediction that about 325 amputations are likely to occur annually in Jeddah compared to 741 in Riyadh and 3970 in KSA. When we applied the results of KSA to those of MENA countries, 44208 amputations were predicted annually.**
***Conclusion:*** **Half a million diabetes-related amputations of the lower extremities are likely to occur in KSA and MENA countries over the coming decade. National registries are urgently needed.**

***Keywords:*** diabetes mellitus, ulceration, amputation, ischemia

## INTRODUCTION

More than 50% of lower limb amputations are performed on diabetic patients.1) Diabetic foot disorders/ulcers (DFD/DFU) are one of the common chronic complications of diabetes, which may lead to major and minor limb loss.2–5) These amputations are usually associated with an extended hospital stay, high mortality and low rehabilitation rates.2,4,5)

On the 10th of March 2009, Dr Abdulaziz Al-Gannass, a foot and ankle surgeon at the National Guard King Abdulaziz Medical City in Riyadh, KSA, told the AFP (Agence-France-Presse) news agency that the number of diabetes-linked amputations is rising quickly and beginning to occur at younger ages. He added that some 90 diabetic amputations are performed monthly, i.e. three per day were performed in the KSA capital of Riyadh.6) This information was published by many newspapers and media sites on the web, sometimes without mentioning Al-Gannass saying that he "could not provide a figure for such cases." This piece of information was continuously quoted by public reporters in media.

In view of the absence of national registry and official data for diabetes-related amputations in KSA and perhaps in most of the Middle East and North African Countries (MENA), it may be the time to challenge the above quoted figures in view of the most recent Saudi official data as reported by the Saudi Ministry of Health and Saudi Central Department of Statistics & Information,7,8) as well as reviewing the author's local data-base4,5) and available data published in the literature9–14) aiming to estimate the magnitude of the problem and forecast the future not only in KSA but perhaps in other similar countries with high

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**Table 1 Population, population at risk of having Diabetes Mellitus (DM) and number of diabetic patients**

| Description | Jeddah | Riyadh | KSA | MENA |
|---|---|---|---|---|
| Overall population ( × 103) (8) | 3456 | 5254 | 27137 | 574115 |
| Population at risk (Aged above 20 years) (15) | 2073 | 3152 | 15186.8 | 344469 |
| Number of diabetics (based on 16.8 comparative prevalence rate) (15) | 348.0 | 529.0 | 2551.0 | 32032 |

KSA: Kingdom of Saudi Arabia; MENA: Middle East and North African

**Table 2 Assumptive prevalence rates of amputations based on estimated numbers of diabetic patients as reported in media[6]**

| Descriptions | Jeddah | Riyadh | KSA | MENA |
|---|---|---|---|---|
| Estimated number of diabetic patients at risk ( × 103) | 348.0 | 529.0 | 2551 | 32035 |
| Assumptive number of amputations based on 0.2% risk for diabetics | 696.0 | 1080 | 5102 | 64070 |

KSA: Kingdom of Saudi Arabia; MENA: Middle East and North African

steadily increasing prevalence rates of diabetes particularly Arab[10] and MENA countries.[15,16] Such data may be used as an indirect indicator or marker for measuring the effectiveness of prevention and management provided to diabetics suffering from foot ulceration. This may also excite policy makers to launch national registries for diabetes-related amputations in KSA and MENA countries, which are confronting an impending health crisis.

## METHODS

### Aim

To estimate the likely annual occurrences of diabetes-related lower extremities amputations and address the need for national registries in KSA and MENA countries.

### Design

In view of the absence of a Saudi national registry for amputations, the author tried to verify if the previously quoted figure in media was correct and generate approximate figures for the prevalence of diabetic amputations. Different calculation formulae were used, based on the most recent information published by our group[4,5] in Jeddah, which is the second largest city in KSA, aiming to predict the total number of amputations performed annually, in all of KSA. Such information is needed as a base-line indicator for effectiveness of health care services provided. It will also help in future health plans and for forecasting the future magnitude of diabetic lower extremities amputations not only in KSA but also in all Arab and MENA countries, which share high prevalence rates of diabetes, and common cultural and social backgrounds.

### Assumption

Based on the figure quoted by Al-Gannass[6] of KSA, a total of at least 1080 diabetes-related amputations (i.e. 90/month) are performed annually in Riyadh, the capital of KSA, which has a population of 5.25 million. This means an incidence rate of 205 amputations per million, 2.0 per 10 000 population, or 1 amputation per 4878 of the total population of Riyadh (1:4878, approximate incidence rate of 0.02% in the overall population). This rate of amputation increases when only the diabetic population in adults is considered. The IDF 2010 comparative prevalence rate of 16.8% of diabetes in KSA general population was used in this study for the sake of standardization of source of Arab and MENA country estimations **Table 1**. The IDF estimated a total of 15.186 million as population at risk of having DM (representing 60% of population above 20 years).[15] This percentage is almost similar to the Saudi MOH report.[7]

The approximate numbers in the population at risk, numbers of diabetics and estimated amputation rates based on the above assumption of amputation rate in capital of KSA are shown in **Table 2** in Riyadh, Jeddah, KSA, and MENA countries. If Riyadh has more than half a million of diabetic patients for whom 1080 amputations were performed, this means simply one amputation will be performed on every 490 diabetic patients (approximately 1:500 ratio) i.e. a prevalence rate of 0.2% in Riyadh diabetics' population. Based on this assumptive rate, one can predict that Jeddah will record 690 amputations/year, KSA 5,102 and MENA countries 64070 amputations/year, **Table 2**.

These above figures will be challenged below using Jeddah's data to reach an estimate of the annual numbers of amputations expected in KSA and MENA countries.

**Table 3 Estimated incidence rates of amputations based on KAUH five years study[4)]**

| Descriptions | | KAUH | Jeddah | Riyadh | KSA |
|---|---|---|---|---|---|
| Based on bed numbers | Number of beds | 650 | 4416 | 11635 | 44099 |
| | (Percentage to KSA capacity) * | (1.26%) | (10%) | (26.4%) | (100%) |
| | Amputation: beds ratio | 1:14 | 1:14 | 1:14 | 1:14 |
| | Number of amputation | 45 | 306.0 | 650 | 3053 |
| Based on operation numbers | Number of Operations ** | 9342 | 89385 | 184852 | 929403 |
| | (Percentage to KSA) | (1.0%) | (9.6%) | (19.8%) | (100%) |
| | Amputation: operations ratio | 1:208 | 1:208 | 1:208 | 1:208 |
| | Number of amputation | 45 | 431.0 | 890 | 4476 |
| Based on admission numbers | Number of admissions | 41227 | 166601 | 425283 | 3042465 |
| | (Percentage to KSA) | (1.4%) | (5.8%) | (14.0%) | (100%) |
| | Amputation: Admissions ratio | 1:916 | 1:916 | 1:916 | 1:916 |
| | Number of amputation | 45 | 182.0 | 464 | 3321 |
| Estimated average numbers of amputations | | 45 | 306 | 668 | 3616 |

KSA: Kingdom of Saudi Arabia; KAUH: King Abdulaziz University Hospital

* Number of beds = MOH beds + Estimate of other sectors [Other sectors = (MOH × 40%)] in Jeddah & Riyadh

** Number of operations = MOH operations + Estimate of other sectors [Other sectors = (MOH × 52.2%)] in Jeddah & Riyadh

### Data Sources

Data from the following sources were reviewed and analyzed aiming to estimate the magnitude of the problem:

- Reported prevalence rates of diabetes by IDF[15)]
- Two previously published studies by the author's group in Jeddah[4,5)]
- Annual report of Saudi Ministry of health 2009[7)]
- Saudi Central Department of Statistics & Information CDSI 2010 national census[8)]

## RESULTS

### Saudi Population

According to the most recent CDSI 2010 national census,[8)] the population in KSA reached 27136977 (including 8429401 expatriates). The Saudi CDSI report also indicated a 3.2% growth rate compared to 2004's census.[8)] It also showed that Riyadh's population is around 5 million (5254560) compared to 3.5 million (3456259) in Jeddah which is the second largest city in KSA.[8)] Forty percent of the population is below 20 years of age,[7,15)] **Table 1.** Based on the above figures, comparisons will be done with studies done in Jeddah and correlate it to Riyadh's incidence rate of 0.2% risk of amputation in diabetics **Table 2.**

### Estimation Methods

*King Abdulaziz University Hospital KAUH, Jeddah Study[4)]*

KAUH is a tertiary care general hospital and has all specialties and sub-specialties. It is the only public university hospital in Jeddah city, with a bed capacity of 650, during the period of our studies (reached 702 lately), which represents 1.26% of the whole KSA bed capacity 55932 beds in all sectors. In 2009,[7)] the total number of surgical operations performed in KAUH was 9342 which represent 1% of the total number performed in the whole KSA 929403. KAUH contributed to all hospitals' admissions in KSA (3.0 million admissions) by admitting 41227 patients i.e. 1.4% of the KSA's admissions.

In a retrospective study over a five year period (January 2004–December 2008), we reported 222 diabetes-related lower limb amputations performed in KAUH. This means that approximately 45 amputations were performed on diabetic patients per annum or 1 amputation to every 14 beds in KAUH (1:14), or 1 amputation in every 208 surgical operations performed (1:208) or 1 amputation in every 916 patients admitted to KAUH (1:916).

In **Table 3,** the previous rates are applied to Jeddah, Riyadh and the whole KSA aiming to predict the number of amputations in Jeddah, Riyadh and the whole Kingdom. The figures obtained are 306, 650 and 3053 amputations respectively based on the amputation: beds ratio

**Table 4** **Estimated incidence rates of amputations based on statistics from 3 major hospitals in Jeddah in year 2008**[5)]

| Descriptions | | KAUH | Jeddah | Riyadh | KSA |
|---|---|---|---|---|---|
| Based on bed numbers | Number of beds | 2052 | 4416 | 11635 | 44099 |
| | (Percentage to KSA capacity) * | (4.6%) | (10.0%) | (26.4%) | (100%) |
| | Amputation: beds ratio | 1:16 | 1:14 | 1:14 | 1:14 |
| | Number of amputation | 128 | 275 | 725 | 2750 |
| Based on operation numbers | Number of Operations ** | 24342 | 89385 | 184852 | 929403 |
| | (Percentage to KSA) | (1.0%) | (9.6%) | (19.8%) | (100%) |
| | Amputation: operations ratio | 1:190 | 1:190 | 1:190 | 1:190 |
| | Number of amputation | 128 | 470 | 972 | 4887 |
| Based on admission numbers | Number of admissions | 72937 | 166601 | 425283 | 3042465 |
| | (Percentage to KSA) | (1.4%) | (5.8%) | (14.0%) | (100%) |
| | Amputation: Admissions ratio | 1:569 | 1:569 | 1:569 | 1:569 |
| | Number of amputation | 128 | 292 | 746 | 5,339 |
| Estimated average numbers of amputations | | 128 | 345 | 814 | 4325 |

KSA: Kingdom of Saudi Arabia; KAUH: King Abdulaziz University Hospital

* Number of beds = MOH beds + Estimate of other sectors [Other sectors = (MOH x 40%)] in Jeddah & Riyadh

** Number of operations = MOH operations + Estimate of other sectors [Other sectors = (MOH x 52.2%)] in Jeddah & Riyadh

at KAUH. These amputation numbers are higher based on operation ratio 431, 890, and 4,476 but lower based on admission ratio 182, 464, and 3321 respectively. The averages for these figures are 306 for Jeddah, 668 for Riyadh and 3616 for the whole KSA. It is obvious, therefore, that the current estimation of 668 is less than the quoted number of 1080 by 38.0%.

*Diabetes-related amputations in three major public hospitals in Jeddah*[5)]

In 2008, the amputations number performed on diabetic patients in 3 major hospitals in Jeddah was 128. The 3 major hospitals had a total bed capacity of 2052 (about 50% of Jeddah's bed capacity) and admitted 72937 patients over one year period. Surgeons performed approximately 24342 operations in all disciplines. Calculations were again done on the same line of previous study, **Table 4.** The averages of the three methods were 345 amputations for Jeddah, 814 for Riyadh and 4325 for KSA.

Finally, averages of three methods in both studies were taken, and it was found that 325 amputations are estimated to be performed annually in Jeddah, compared to 741 in Riyadh and 3970 for the whole kingdom i.e. 2.5 amputations per 10000 population. Again, this figure is less than the one quoted by 31%, **Table 5.** When applied to MENA countries, 44208 amputations are predicted annually.

## DISCUSSION

Diabetes is the global epidemic of the 21st century. The number of adults with diabetes in the world was 135 million in 1995. At present, 366 million people are affected by diabetes worldwide and 80% of them live in low and middle-income countries.[16)] By 2030, the global burden of diabetes is projected to increase to 552 million people.[16)] Between 2010 and 2030, there will be a 69% increase in the number of adults with diabetes in developing countries and a 20% increase in developed countries.[17)]

Data that has been accumulated over the last three decades confirms an epidemic of type 2 diabetes in KSA.[11)] KSA is one of the top ten countries (number 6) for prevalence of diabetes and is expected to continue in the coming two decades with prevalence rate of 20.0% in the age group 20–79 years.[16)] Other countries in the "top-ten" included Kuwait 21.1, Lebanon 20.2, Bahrain 19.9 and United Arab of Emirates 19.2 as reported by IDF recently.[16)] The published diabetes mellitus DM prevalence rates in KSA vary. These rates are still not well known due to various methodologies used by researchers.[10–12,15,16)] For instance Al-Nozha et al.[12)] conducted a national survey and reported a prevalence rate of 23.7% in the adult Saudi population above 30 years of age (26.2% in males versus 21.5% in females). In contrast, Elhadad et al.[11)] reviewed all of studies and commented that the last rate is somewhat inflated. The International Diabetes

**Table 5** Summary of estimated incidence rates of amputations based on averages obtained by the three methods of analysis

| Description | Jeddah | Riyadh | KSA |
|---|---|---|---|
| Assumption * | 696 | 1,080 | 5102 |
| Method 1 averages ** | 306 | 668 | 3616 |
| Method 2 averages *** | 345 | 814 | 4325 |
| (Both studies averages) | 325 | 741 | 3970 |

KSA: Kingdom of Saudi Arabia
* Table 2, ** Table 3, *** Table 4

Federation IDF in 2010 reported a comparative prevalence rate of 16.8% in the age group between 20–79 years.[15] In this study, the IDF prevalence rate of 16.8% of diabetes in the general population of KSA was used[15] as it is more conservative and was generated by an international body after a review of various published studies. It is closer to the period during which previous studies of the population of Jeddah were performed.

Diabetes-related lower-extremity amputations rates are important indicators for the effectiveness of health care provided to diabetic patients including prevention and management of foot ulcers and to forecast the magnitude of the problem. Unlike developed countries where data on the incidence of amputations can be obtained relatively easily,[18] these rates are unknown in most of developing countries, which record high prevalence of diabetes such as KSA and MENA countries. Amputationfigures require very careful interpretation. Variations in the definition of amputation (i.e. major, above ankle; or minor, distal to ankle), selection of the population, and the choice of numerator and denominator make it difficult to perform comparisons. In addition to disease severity, many aspects of the structure of care services affect this decision, including access to primary care, quality of primary care, delays in referral, availability and quality of specialist resources, and prevailing medical opinion. It follows that a high incidence of amputation can reflect a higher disease prevalence, late referral, limited resources, or a particularly interventionist approach by a specialist team.[18] In KSA and perhaps most of MENA countries cultural, social and individual patient factors play a major role on the amputations' decision. This makes cross comparison between different data more complicated. However, amputations' rates will definitely help as a base-line indicator[19] in the same country or similar countries that share racial and cultural backgrounds, and health care systems, such as those of MENA countries. The current study aims to raise the level of awareness in these countries about the need for national registries for amputations among diabetics who represent 20% of their nations.

It is estimated that 325 amputations are likely to be performed in Jeddah compared to 741 in Riyadh and 3970 for the whole kingdom. These figures are less than the one quoted in media by 31%. This means an incidence rate of 2.6 per 10000 people at risk. This rate is on the low side but within the range published in industrialized countries, which ranged from 0.06 to 3.83 per 10 (3) people at risk.[18] The figures generated in the current study are for all amputations i.e. major and minor. According to our previous studies, major amputations accounted for 45%[4]and 38%[5] i.e. average of 41.5% are majors. Based on the current data, it can be predicted that 1647 major amputations are performed annually in KSA.

Up to my knowledge, this is the first report which tried to predict the magnitude of the diabetes-related lower-extremity amputations rates in KSA and MENA countries and to challenge the figures quoted in media. However, it is still a "snapshot" on a complex health problem. However, there are significant limitations in this exercise. Firstly, it is based on the two studies of the author's group. One of the two studies[4] was a retrospective single center study, and the second,[5] a multi-central study. However, it was not as comprehensive as the others because it was conducted in only three major hospitals in Jeddah. Secondly, amputation figures were generated by diverse methods, which included amputations per hospital beds, per operations and per admissions. The second reason may be a point of strength rather than weakness as using multiple methods of calculations will reduce the possibility of bias when only one variable is used. Finally, whatever is done will not replace the accurate data collection in a prospective setup.

Intended future registries will hopefully establish, not only the overall future trends of amputation in general, but also the high-low amputation ratio, i.e. the major: minor ratio, which is important in proper evaluation of improvements in care organization and multidisciplinary-centered protocols.[19,20] Similar to developed countries[21] such registries will give opportunities for cross-national learning to improve health system performance. It will also help in assessing the outcomes of newer modalities of treatment.[22–24]

This work shows the difficulty and shortcomings of scattered data in the literature and will support the timely need for accurate data-base sources. United Nations Resolution 61/225, has already adopted unanimously in 2006, recognizes diabetes as a serious and costly disease that poses a threat to individual well-being and economic progress, especially in low- and middle-income countries.[25] It also addressed the problems of data accuracy in less-developed countries by stating "In view of absence of transparency, public health services, national registries, national diabetes programs and national well-designed community studies, most of the available published data including those published by recognized international bodies are not accurate".[25]

In conclusion, half a million of MENA country citizens are likely to have a minor or major diabetes-related amputations according to the figures generated in the current study of KSA. Most of the amputees will not be rehabilitated and may lose their jobs or incomes. In view of this, national registries are urgently needed in KSA and MENA countries.

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**Original Article**

# Surgical Procedures for Renal Artery Aneurysms

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Takahiro Toyofuku, MD, PhD

***Objective:*** **The aim of this study was to assess the strategy and surgical procedures for treating a renal artery aneurysm (RAA).**

***Patients and Methods:*** **We retrospectively reviewed the surgical strategy for 21 cases with RAA between 2001 and 2010 at this institution. Treatment was indicated for patients with an RAA larger than 2 cm and/or symptoms. Surgical treatment was the initial strategy, and coil embolization was indicated in the case of narrow-necked, saccular, extraparenchymal aneurysms.**

***Results:*** **Fifteen patients in 21 cases received an aneurysmectomy and renal artery reconstruction with an in-situ repair. One patient underwent an unplanned nephrectomy, and coil embolization was performed in 5 patients.**

***Conclusion:*** **In-situ repair was safe and minimally invasive. RAA, even in the second bifurcation, could be exposed by a subcostal incision, and the transperitoneal approach permitted the safe treatment of an RAA with acceptable results, in our simple preservation of renal function.**

***Keywords:*** renal artery aneurysm, patch angioplasty

## INTRODUCTION

Renal artery aneurysms (RAAs) are uncommon. They are often identified incidentally during abdominal computed tomography (CT) screening for other diseases. In recent years, coil embolization or stent-graft with the coil embolization was successful for treating RAAs, but complex aneurysms may require aneurysmectomy and renal artery reconstruction by in-situ repair or ex-vivo. The aim of this study is to assess the strategy and surgical procedures for RAA in this institution.

## PATIENTS AND METHODS

This study retrospectively reviewed the surgical strategy applied in 21 cases with RAAs between 2001 and 2010 in the department of Vascular Surgery of Tokyo Medical and Dental University. RAAs were diagnosed using CT and angiography, to assess the type of aneurysm, size, lesion, and association with branches of the renal artery. Renal function was evaluated using serum creatinine (Cr), the estimated glomerular filtration rate (eGFR) and renogram. Surgical treatment was indicated for patients with RAAs larger than 2 cm in diameter and/or symptoms (hematuria, back pain, uncontrolled hypertension in patients using antihypertensive drugs) and coil embolization was indicated in that case of narrow-necked, saccular, extraparenchymal aneurysms. The operation in in-situ repair was performed by subcostal incision and transperitoneal approach, and mannitol (0.5 g/kg) was administered before renal artery cross-clamping to preserve renal function.

The branches of the renal artery were reconstructed using the pantaloon technique or end-to-end and end-to-side fashion when that case of the diameter of the renal artery branch with two branches was greater than 2 mm, and renal artery branch was sacrificed when the diameter of the branch was less than 2 mm. Operating time, blood

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**Table 1 The profile in 21 patients**

| | (n = 21) |
|---|---|
| gender (m:f) | 11 : 10 |
| Location | right: 10, left: 11 |
| Size (mm) | 28 ± 12 |
| Asymptomatic patients | 16 |
| Symptom | pain: 5 |

**Table 2 Operative procedures**

| Procedures | (n = 21) |
|---|---|
| ex-vivo repair→unplanned nephrectomy | 1 |
| in-situ repair | 15 |
| patch plasty | 6 |
| primary closure | 2 |
| end-to-end anastomosis with pantaloon | 2 |
| end-to-end anastomosis with side-to-end | 2 |
| end-to-end anastomosis | 1 |
| end-to-end anastomosis with ligation | 1 |
| aorto-ePTFE graft interposition | 1 |
| coiled embolization | 5 |

**Table 3 Procedures**

| procedures | in situ repair (n = 15) | Patch plasty (n = 6) |
|---|---|---|
| operation time (min) | 209 ± 49 | 237 ± 38 |
| operative blood loss (ml) | 368 ± 261 | 447 ± 259 |
| warm ischemic time (min) | 27 ± 20 | 26 ± 9 |

loss, warm ischemic time, cold ischemic time and renal function between pre-operation and post operation were evaluated. All values are expressed as the mean ± SD. The Mann-Whitney U test and paired t-test were used to evaluate the differences in variables. A p value less than 0.05 was considered to be a statistically significant difference.

## RESULTS

There were 21 cases that included 11 males and 10 females with an average age of 62 ± 10 years, (range: 37–72 years). The RAAs ranged from 12 mm to 60 mm in diameter. All were saccular aneurysms (**Table 1**).

In-situ repair was done in patients with the RAA, even if the RAA was located at the second bifurcation. Fifteen patients underwent an aneurysmectomy and renal artery reconstruction with in-situ repair via a subcostal transverse incision. Moreover, an ex-vivo operation was initially attempted in one patient. However, an unplanned nephrectomy was performed because the RAA had a diameter of 60 mm and involved four second branches and renal hypertension could have developed if renal branches were reconstructed.

Surgical procedures were assessed. Many aneurysms were located between the first and second bifurcation. An aneurysmectomy and primary direct closer or patch angioplasty were usually performed if the renal artery aneurysm did not involve many renal branches (**Table 2**).

The operating time, warm renal artery clamping time and blood loss were 209 ± 49 min (median: 212), 27 ± 20 min (median: 25) in fifteen cases, excluding the unplanned nephrectomy and 368 ± 261 mL, respectively (**Table 3**). The postoperative course was uneventful in all cases. Moreover, Crs before and after the operation were 0.78 ± 0.2 and 0.75 ± 0.3 mg/dl, and eGFRs, 71 ± 16, 78 ± 28 mL/min/1.73m$^2$, in 15 cases that underwent a aneurysmectomy and renal artery reconstruction. Renal dysfunction was not significantly different. In addition, the primary patency rates in 15 reconstructed renal arteries with RAA were 100%, during a mean follow-up period of 32 ± 19 months (range, one month to 71 months).

Coil embolization was performed in 5 patients due to narrow-necked, saccular renal artery aneurysms, which were located at the first bifurcation of the renal artery. Those aneurysms were treated by coil exclusion of the aneurysmal sac using platinum Guglielmi detachable coils (GDCs 18 Boston Scientific, USA) or Interlocking detachable coils (IDCs Boston Scientific, USA) delivered through a microcatheter and no stents were used in five cases. An assisted balloon catheter (Attendant$^{\text{TM}}$ 4.5 × 10 mm) was used to decrease blood flow in one case. Five patients were successfully treated without complications, renal insufficiency, or nephrectomy. The Cr values before operation and after operation were 0.78 ± 0.2 and 0.75 ± 0.3 mg/dl, respectively. There was a mean follow-up period of 24 ± 25 months (range one month to 67 months).

## DISCUSSION

The RAAs were relatively rare, and the prevention of rupture was the most common indication for treatment of an asymptomatic RAA. Generally, the repair of a renal artery aneurysm has been recommended for aneurysms greater than 2.0 cm in diameter, with symptoms such as flank pain or hematuria, or renovascular hypertension due to the aneurysm.[1–4] The RAAs of this studies were located in all but the first bifurcation to second bifurcation most of the patients in this series as well as in the reports by and another group.[2,5–7] And we could expose renal arteries by subcostal incision and transperitoneal approach much easily than by median incision.

An end-to-end anastomosis or graft interposition was used depending on the location, and an end-to-end anastomosis with pantaloon, side-to-end anastomosis or branch ligation is used in case the artery feeds a small area or the diameter of the branch is less than 2 mm. Sometimes, the aortorenal bypass is done using a saphenous vein or ePTFE graft to shorten renal warm ischemic time.[8]

This patch angioplasty was done in another group.[9,10] Pfeiffer et al.[9] reported no recurrence of aneurysms to be observed after tailoring in their series, and this may be because the aneurismal parts of the vessel wall were resected, leaving almost normal arterial wall next to the orifices of the branches. However, the mean follow-up period in the tailoring group was only 34.9 months, in comparison to 46 months for the entire series; therefore, tailoring could not be assessed sufficiently in terms of recurrent aneurismal dilatation with the current data. Patch angioplasty was applied in 6 cases in our study. This study was small numbers' group but warm ischemic time was 27 ± 20 min (n = 6), so these operations were accomplished with acceptable results in patch angioplasty and another way in this study. Patch angioplasty might be acceptable to prevent a portion of the suture to be narrow, in cases where the aneurysm is located in the first to second bifurcation of the renal artery.

A cold (4°C) renal perfusate of lactated Ringer's solution and administration of mannitol was used to cool the kidney and reduce the risk of acute renal tubular necrosis.[2,9,11] Our study also did as well for renal preservation. Moreover, cooling of the kidney should be repeated if the reconstruction requires more than 30 minutes of ischemic time. A cold (4°C) Ringer's solution of 40 mL was administered into the artery and 20–30g mannitol(0.5 g/kg) was administered before declamping the renal artery to reduce acute renal tubular necrosis in our study as well as in another study.[11] Renal function could be preserved in these simple procedures.

There have been few recent reports of coil embolization for RAA, though the standard therapeutic method for IVR has been established.[12–17] Endovascular therapy with coil embolization and preservation of renal blood flow may be considered as a realistic alternative surgery in narrow necked, saccular, or extraparenchymal aneurysms.[12] However, there are no reports that confirm an RAA was thrombosed, whether or not the expansion or rupture of RAA was prevented. The long-term results of coil embolization are not reported. So our follow-up period was only 19 ± 28 months, we need to follow-up for many years. In addition, occlusion of the renal artery from migration of coils is a major complication associated with embolization.[14] There has been no rupture, enlargement of the RAA and no renal dysfunction in the current series, and renal flow has been maintained. However, a careful follow-up is required for such RAAs.

## CONCLUSION

This study assessed the surgical treatment of RAAs in this institution. RAA, even in second bifurcation, could be exposed by a subcostal incision, and the transperitoneal approach permitted the safe treatment of an RAA with acceptable results in our simple preservation of renal function.

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**Original Article**

# Non-Contrast Renal MR Angiography: Value of Subtraction of Tagging and Non-Tagging Technique

Takehiro Shimada, MD, Makoto Amanuma, MD, Ayako Takahashi, MD, and Yoshito Tsushima, MD

***Purpose:*** **The aim of this study was to examine the usefulness of the subtraction technique of non-contrast renal magnetic resonance angiography (MRA) between tagged and non-tagged data collection.**

***Material and Methods:*** **We performed renal MRA on eleven healthy volunteers using a 3T MRI unit. For renal MRA, a three dimensional balanced type steady-state free precession (SSFP) sequence (True FISP, Siemens) was used with diaphragmatic navigator gating. We tried to acquire selective arterial images by subtracting black-blood images (tagged images, on which arterial longitudinal magnetization was nearly zero by selective inversion of upper-stream aortic flow) from bright-blood images (non-tagged images, on which arterial flow is bright due to inflow effect). For analysis, two radiologists independently evaluated the visual quality of the axial and coronal targeted maximum intensity projection images (MIP) of original bright-blood MRA and subtraction MRA.**

***Results:*** **Visualization of the main stem of the renal arteries and their 1st branches were satisfactory on both techniques, and there was no statistically significant difference. The score of 2nd branch appeared superior with the subtraction method, but only the right side showed a statistically significant difference ($P<0.01$). Visualization of small intraparenchymal arteries was significantly superior with subtraction method on both sides.**

***Conclusion:*** **We tried to improve selective demonstration of renal arterial branches using subtraction technique. Although full sequence optimization was not performed, this pilot study showed this technique to be slightly time-consuming but superior in visualization of peripheral branches and possibly more sensitive in detecting small vessel abnormalities.**

***Keywords:*** magnetic resonance angiography (MRA), renal artery, non-contrast technique, 3T MRI, SSFP imaging

## INTRODUCTION

In the diagnosis of renal artery stenosis, catheter angiography has been considered the gold standard, but contrast-enhanced computed tomographic angiography (CTA) and magnetic resonance angiography (MRA) have replaced it in recent years.[1–3] Catheter angiography is a highly invasive technique, and iodinated contrast materials carry the risk of side effects such as renal toxicity and allergic reactions.[4] Gadolinium contrast agents also carry the risk of acute side effects, and NSF (nephrogenic systemic fibrosis) is also a concern in patients with renal dysfunction.[5,6]

More recently, MRA without contrast agents has become increasingly common in the clinical setting, not only in head and neck region, but also in the body and extremities.[7,8] Excellent image quality has been reported in renal MR angiography on 1.5T MR units, and the

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**Table 1 Imaging parameters for steady-state free perception**

| | |
|---|---|
| TR/TE/FA | 1.4/1.68/90 |
| TI | 1.28 sec |
| receiver bandwidth | 783 Hz/pixel |
| slab thickness | 100 mm |
| slice thickness | 0.9 mm |
| field of view | 251 × 350 mm |
| resolution | 0.9 × 1.15 × 1.27 |
| parallel imaging factor | 2 |

usefulness of MRA of the head in higher field units has been established.[9] Lanzman et al. reported the usefulness of non-contrast renal MRA performed on a 3 Tesla unit.[10,11] The report suggests superior image quality in higher field units is due to both an increase of blood signal and a decrease of retroperitoneal tissue signal. Blood flow signal from the inferior vena cava and renal vein are suppressed by inversion pulses, but inadequate suppression may occur in some cases due to higher velocity blood flow. These may increase signal intensity around the renal arteries, impairing depiction of peripheral branches on non-contrast MRA.

In contrast-enhanced MRA, subtraction technique between 3D slabs before and after contrast administration is routinely performed for improving vascular visualization.[12,13] In this technique, if data acquisition timing is not optimal and renal parenchyma becomes enhanced, selective visualization of the renal artery is impeded. However, with appropriate data acquisition timing, excellent selective visualization is possible. On the other hand, the subtraction technique is also feasible on non-contrast MRA, by obtaining images with and without tagging of upper-stream arterial flow.[14] Subtraction MRA may, in fact, be more suitable for this technique than contrast-enhanced MRA, because there is no major difference in the renal parenchyma signal between images with and without flow tagging for the former. The aim of this study was to examine the usefulness of subtraction technique of non-contrast renal MRA.

## Material and Methods

This study was approved by our institutional review board, and informed consent was obtained from all subjects.

We performed renal MRA on eleven healthy volunteers (seven men and four women; age range, 24–49 years; mean age 30.6 years; body weight range, 45 to 80 kg; mean, 60.3 kg) using a 3T MRI unit (Magnetom Trio 3T, Siemens AG, Erlangen, Germany) in Gunma University Hospital from March 2011 to May 2011. An eight-channel phased array coil was used with a spinal matrix coil. For renal MRA, a three dimensional steady-state free precession (SSFP) sequence (True FISP, Siemens) was used with diaphragmatic navigator gating. For navigator gating, a two-dimensional selective pencil-beam excitation pulse was used to detect the position of the right hemidiaphragm during normal breathing. Data were obtained during expiration, during which diaphragmatic motion would be minimal. Navigation pulses were placed to avoid excitation of the right kidney.

Detailed imaging parameters are shown on **Table 1**. For all MRA studies, a single three-dimensional slab was placed in a transaxial plane. We tried to acquire selective arterial images by subtracting black-blood tagged images from bright-blood non-tagged images. The bright-blood images are the same as those of the commonly used non-contrast MRA technique, depicting the arterial flow entering the imaging slab as high signal. Background signal suppression was performed by a selective inversion pulse covering the slab. After the 180-degree pulse, the background static tissue recovers and its longitudinal magnetization decreases toward the null point. To suppress the fat tissue signal, an additional frequency selective fat saturation pulse was applied just before data acquisition. The black-blood images were acquired in an identical manner, except for additional suppression of arterial inflow by applying a tagging pulse covering the heart.

The resulting time interval between the first inversion pulse and effective echo time was set at 1280 msec.[15,16] Finally, we subtracted the two image sets, and visualization of renal arterial branches was subjectively analyzed.

For analysis, two radiologists independently evaluated the visual quality of the axial and coronal MIP image set. Original bright-blood MRA and subtraction MRA were mixed and randomly ordered for evaluation. The image quality was evaluated at four segments: a) main trunk of renal artery; b) 1st branches (ventral and dorsal branch); c) 2nd branches; d) arcuate arteries. The quality of visualization was scored using a three-point-scale: 3, continuity and luminal dimension of artery can be evaluated with confidence; 2, artery is depicted, but difficult to evaluate continuity and luminal dimension with confidence; 1, poor (arteries are not visible or difficult to evaluate). Statistical comparison was made with Wilcoxon rank test. A P-value less than 0.05 was considered statistically significant.

**Table 2 Statistical evaluation of visualization score**

| Part of renal artery | Right main trunk | Left main trunk | Right 1st branch | Left 1st branch | Right 2nd branch | Left 2nd branch | Right arcuate artery | Left arcuate artery |
|---|---|---|---|---|---|---|---|---|
| bright-blood mean score | 2.73 | 3.00 | 2.36 | 2.73 | 1.82 | 2.00 | 1.18 | 1.18 |
| subtraction mean score | 3.00 | 2.91 | 2.64 | 2.82 | 2.36 | 2.36 | 1.91 | 1.64 |
| *P* value | NA | NA | NA | NA | <0.01 | NA | <0.01 | <0.01 |

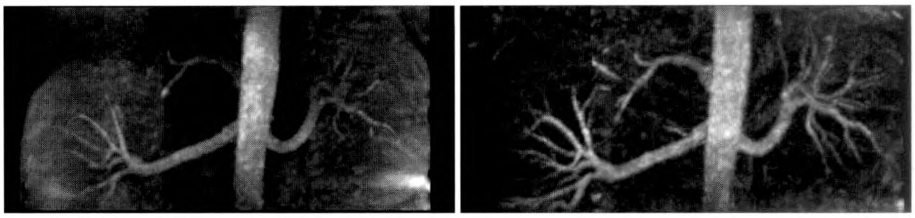

**Fig. 1** 30 year-old male volunteer. Coronal maximum intensity projection (MIP) images of original bright-blood MRA (**a**) and subtraction MRA (**b**). Though main trunk and 1st branches of renal arteries in both images are depicted equally, 2nd and more peripheral branches are more clearly demonstrated on subtraction MRA.

## RESULTS

Visualization of the main stem of the renal arteries and their 1st branches were satisfactory on both techniques, and there was no statistically significant difference. The score of 2nd branch appeared superior with the subtraction method, but only the right side showed a statistically significant difference ($P < 0.01$). **Table 2** shows the results of statistical evaluation of visualization score. Visualization of small intraparenchymal arteries was significantly superior with subtraction on both sides (**Fig. 1**). High intensity of the inferior vena cava was seen in six out of eleven cases on bright-blood images, overlapping and sometimes obscuring the 1st or 2nd branches of the right renal artery on coronal images. On the other hand, there was no observable signal from the inferior vena cava on subtraction images (**Fig. 2**). Actual imaging time of bright-blood images and black-blood images were 6:29 to 9:35 (mean time 7:59) and 5:27 to 11:02 (mean time 7:28).

## DISCUSSION

The renal artery is a major branch of the aorta, and various vascular lesions may develop in this vessel. Renovascular hypertension is most frequent cause of secondary hypertension, and diagnosis of the disease is very important clinically.[17] Atherosclerotic renal artery stenosis tends to induce a narrowing of the main stem lumen,[18] while fibromuscular dysplasia usually involves the distal part of main stem.[19] Polyarteritis nodosa occurs in the peripheral branches of the renal artery.[20] Thus, it is important to visualize the entire renal artery, including the small intraparenchymal branches.

Three-dimensional fast gradient echo with contrast media has been the mainstream of renal MRA. However, since nephrogenic systemic sclerosis (NSF) associated with the use of gadolinium contrast agents has been widely reported, it is virtually impossible to use contrast agents in patients with renal impairment.[5,6] While renovascular hypertension caused by renal artery stenosis does not necessarily lead to renal failure, atherosclerosis is the most common disease of the systemic arteries, making it a frequent cause of renal impairment.

Non-contrast MRA appears attractive as a solution of these problems. Recent developments of non-contrast MRA techniques are remarkable. In addition to the conventional time-of-flight and phase contrast techniques, use of the ECG-gated partial-Fourier fast spin echo technique for evaluating the upper and lower extremity arteries has become clinically widespread.[7,8] In renal MRA, the steady-state data collection described above, combined with respiratory gating, can provide high-resolution blood vessel images without respiratory movement.[16,21–25] We tried to completely suppress the

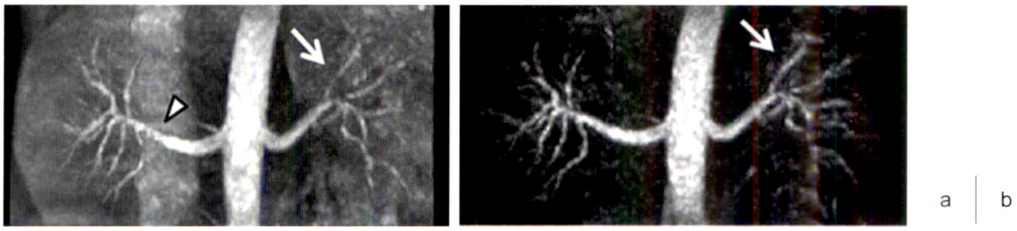

**Fig. 2** 29 year-old female volunteer.
Coronal MIP image in the original image (**a**) demonstrates a focally obscured right renal arterial main stem due to overlapping IVC (arrowheads). On the other hand, the continuity of both renal arteries is preserved at subtraction image (**b**).
The continuity of 1st and other peripheral branch of left renal artery is better depicted in subtraction image compared with bright-blood image (white arrows).

background signal of both images before subtraction. If the imaging slabs were completely identical, the signal suppression of venous structure or renal parenchyma before subtraction would not be so important. However, to avoid possible misregistration or intestinal peristalsis between images, we thought it would be best if the background signal were reduced as much as possible, even before the subtraction.

In this study, although the proximal renal arterial segments were readily demonstrated on the conventional technique, smaller peripheral branches were more confidently evaluated on subtraction images. The results were considered to be due to superior background suppression and resulting higher contrast on subtraction MRI.

The major drawback of the subtraction method is prolongation of imaging time. Simultaneous imaging of black-blood images and bright-blood images by interleaved mode would be desirable but unrealistic due to the nature of the steady-state technique, and two different acquisitions are needed. Gross patient motion between the two sets of images would cause spatial misregistration, resulting in artifacts possibly interfering with image assessment. However, the signal of renal parenchyma is not necessarily high, and the signal of surrounding adipose tissue is well suppressed, making misregistration effect considerable enough to prevent depiction of vessels less likely to occur. The problem of imaging time may eventually be overcome by more advanced hardware or more sophisticated data acquisition techniques.

There are several limitations in this study. All subjects were healthy and relatively young. Non-contrast MRA depends on the flow velocity of target vessels, but renal artery flow tends to be slower in patients (including but not limited to those with renal impairment). Furthermore, the success rate of navigator gated MR images tends to lower in patients and the elderly. Therefore, misregistration artifact due to respiratory gating would likely be higher in the actual clinical setting.

Second, the timing of inversion pulse application was not optimized on this study. Although we used the same imaging parameters both for bright blood and black blood images, optimal parameters would not necessarily be identical. The bright blood technique requires increased signal of distal branches, so a longer TI time may be suitable. On the other hand, the black blood technique requires the perfect nulling of arterial signal, so a shorter TI might be preferable. Detailed optimization would be necessary for actual clinical use, and we are currently investigating sequence optimization.

## CONCLUSION

We tried to improve selective depiction of renal MRA with subtraction. Although it is slightly time-consuming and its clinical utility may be currently limited, it provides superior visualization of peripheral branches even in this pilot study. Further sophistication of the technique would make it even more sensitive in detecting small vessel abnormalities and promising for clinical use.

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**Original Article**

# Clinical Results of Endovascular Abdominal Aortic Aneurysm Repair in Patients with Renal Insufficiency without Hemodialysis

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***Objective:*** **Chronic renal insufficiency may be a relative contraindication to endovascular aneurysm repair (EVAR) for the use of contrast enhanced mediums. It is thought that more contrast enhanced media are needed in patients who are not anatomically suitable for EVAR, because of procedural difficulties. We reviewed a 2 year EVAR experience at our institution to determine whether the procedure and use of contrast enhanced mediums has any deleterious effect on renal function in patients with pre-existing chronic renal insufficiency.**

***Materials and Methods:*** **EVAR was performed in 46 patients with pre-existing chronic renal insufficiency without hemodialysis. Patients were retrospectively assigned to two groups on the basis of their preoperative creatinine clearance levels. Furthermore, patients were assigned to two other groups on the basis of anatomical suitability for EVAR. The absolute change in the serum creatinine (Cr) level was reviewed in the each renal insufficiency group between the preoperative and post-operative time periods.**

***Results:*** **No increase in the serum Cr level was noted, and no patient required temporary or permanent hemodialysis, in any of the groups.**

***Conclusions:*** **EVAR with contrast agents can be accomplished in patients with chronic renal insufficiency without hemodialysis; therefore,elevated Cr levels maynot be a contraindication in EVAR.**

***Keywords:*** endovascular, aneurysm, renal insufficiency, contrast enhanced medium

## INTRODUCTION

Over the past decade, endovascular aneurysm repair (EVAR) with intra-arterial contrast enhanced mediums has become the predominant method in the treatment of infrarenal abdominal aortic aneurysms (AAA). Despite recent, prospective studies that have demonstrated better outcomes after EVAR in the perioperative and intermediate time periods, concerns remain about the long-term durability and safety of EVAR.[1–6)]

EVAR requires intra-arterial administration of contrast enhanced mediums, which can cause impaired renal function, leading to end-stage renal disease. The incidence of contrast-induced acute kidney injury is low (2%) in the general population, but it is high in serum creatinine (Cr) at-risk groups of patients.[7)] One patient population at increased risk for perioperative complications after open or endovascular repair is the group with baseline renal insufficiency. Renal insufficiency is a well-recognized complication after open aortoiliac aneurysm repair.

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However, the effects of EVAR on renal function in these patients remain uncertain. Chronic renal insufficiency is a relative contraindication in the use of intra-arterial contrast enhanced mediums and is thought to further increase the risks of EVAR. Although recent studies have shown that progressive renal dysfunction may develop in patients after EVAR, data are conflicting with regard to the effects of EVAR on renal function compared with standard open repair.[8–10]

In addition, EVAR is usually possible if patients have the appropriate anatomical morphology. It is thought that more contrast enhanced media is needed for patients who were not suitable for EVAR, because their procedures are more difficult and additional devices are used.

The purpose of this study was to compare the effects of EVAR on renal function in patients with pre-existing renal insufficiency. We reviewed a 2 year experience with EVAR at our institution to determine whether the procedure, when performed with intra-arterial contrast enhanced mediums, has any deleterious effects on the renal function in patients with pre-existing chronic renal insufficiency.

## MATERIALS AND METHODS

From April 2009 to March 2011, patients with an AAA larger than 5 cm in diameter, with and without iliac involvement, were eligible for EVAR. Patients at high risk, with severe cardiopulmonary disease, hostile abdomen, or other major comorbid conditions, were offered treatment with a variety of commercial endografts, including the Excluder (W. L. Gore & Associates, Flagstaff, Ariz), Zenith (Cook, Bloomington, Ind) and Powerlink System (Endologix, Irvine, Calif).

We performed EVAR using the almost same procedure that has been described previously.[11] Distal fixation sites were usually the common iliac artery. MReye embolization coils (Cook) were mostly used to exclude flow to the hypogastric arteries intraoperatively when the distal fixation site was the external iliac artery.

In patients with chronic renal insufficiency, perioperative intravenous hydration with 0.5–1L of normal saline solution plays a well-established role in reducing the risk of nephropathy induced by contrast medium. In addition, the administration of all nephrotoxic drugs was discontinued. Non-ionic contrast medium Iohexol (Omnipaque 300), thought to be the more suitable contrast medium, was used.[7] Furthermore, to minimize the cumulative nephrotoxic effects of intravascular contrast agents, intraoperative imaging, including arteriography and intravascular ultrasounds (Volcano s5 Imaging System), were used for target site identification, landing zone measurement, neck quality analysis, preprocedural quality assessment, and trouble-shooting during EVAR.[12]

A retrospective review was performed from the charts, surgical reports, and laboratory data of these patients. In the initial post-operative period, the serum Cr was measured on post-operative days 1, 2 and 7. Patients with worsening renal function, illustrated by an increase in serum Cr, were observed for daily serum Cr measurement until acute tubular necrosis resolved or improved. Creatinine clearance (CCr) indicated the measure of glomerular filtration rate (GFR), and was calculated with the Cockroft-Gault formula: $\text{CCr} = (140 - \text{Age}) \text{ x Weight (kg) } (0.85 \text{ if female}) / (72 \times \text{Serum Cr [mg/dl]})$.[13]

Patients were retrospectively assigned to two groups based on their preoperative CCr: group I (n = 31) who had CCr 30 to 50 mL/min and group II (n = 15) who had CCr less than 30 mL/min. None of the patients had a history of hemodialysis. Exclusion criteria included chronic renal insufficiency requiring hemodialysis, and symptomatic high-grade renal artery stenosis requiring renal angioplasty and stenting. And the patients were excluded if there was coiling of hypogastric arteries the day before operation.

EVAR is usually possible if patients have appropriate anatomical morphology. Patients who were suitable for EVAR have been thought to have a reduced procedural length, fewer transfusion requirements, and less morbidity.[14] In a different viewpoint, we then further divided the patients into two groups according to the anatomical suitability criteria, which included an aortic neck diameter of 18–28 mm, neck length more than 15 mm, neck angulation less than 60 degrees, iliac diameter of 7.5–20 mm, and a length of the iliac sealing zone more than 10 mm. Relative contraindications to endovascular repair, such as the thrombus load within the aortic neck were not considered.[14] Patients who have appropriate anatomical morphology for EVAR were included in group A (n = 25), the other patients were included in group B (n = 21).

Statistical analyses were performed with the t-test and Fisher's exact test, and statistical significance was defined when the P value <0.05.

## RESULTS

Forty-six patients with renal insufficiency who were

**Table 1**

| Factors | GroupI 30≤CCr<50 (N = 31) | GroupII CCr<30 (N = 15) | P value |
|---|---|---|---|
| Age(years) | 78.2 | 82.0 | N.S. |
| DM(%) | 19.4 | 13.3 | N.S. |
| AAA size(mm) | 55.2 | 55.8 | N.S. |
| Operative time(min) | 165.8 | 141.7 | N.S. |
| Contrust agent(mL) | 100.2 | 92.7 | N.S. |

DM: diabetes mellitus; AAA: abdominal aortic aneurysm

not receiving hemodialysis underwent EVAR using an intra-arterial contrast enhanced medium over the 2 year period. The mean follow-up was 6.3 months.

All patients had pre-existing chronic renal insufficiency with baseline CCr of either 30 to 50 mL/min (group I) or less than 30 mL/min (group II). The average patient age was 79.4 years. Co-morbid conditions included diabetes mellitus (8 of all 46 cases; 17.4%). The mean diameter of the AAA was 55.4 mm. A total of 25 cases were treated with Excluder (W. L. Gore & Associates, Flagstaff, Ariz); 19 cases, with Zenith (Cook, Bloomington, Ind); and 2 cases, with the Powerlink System (Endologix, Irvine, Calif). Six patients had an aortoiliac aneurysm that extended to the iliac bifurcation, so coil embolization of the hypogastric artery was performed with MReye embolization coils (Cook), intraoperatively.

The mean intraoperative contrast agent administration was 97.7 mL during EVAR. The preoperative aneurysm diameter, duration of surgery, prevalence of co-morbid conditions, and amount of intraoperative contrast agent administration are summarized in **Table 1**.

Changes in renal function were evaluated by comparing preoperative with the latest available postoperative serum Cr. Patients with a 20% or greater increase in serum Cr were not recognized. Five patients with a 10% or greater increase in serum Cr were defined to have impaired renal function.

The absolute change in serum Cr in the each renal insufficiency group between the post-operative and preoperative time periods was similar (**Table 1** and **Fig. 1**).

We hypothesized that patients who were identified as being unsuitable for EVAR (group B, n = 21), based on anatomical criteria, needed a larger volume of intraoperative contrast agent compared with patients having suitability for EVAR (group A, n = 25). Contrary to our hypothesis, differences in the volume of contrast needed did not reach statistical significance among the groups. Significantly fewer additional devices, such as an aortic extension graft and a bare stent, were needed for patients with anatomical suitability for EVAR (group A) (0.7 versus 1.5: P = 0.02). In patients who were anatomically suitable for EVAR (group A), the CCr tended to be higher in the preoperative period (38.1 mL/min) compared with the group of patients who were deemed anatomically unsuitable for the procedure (group B) (33.8 mL/min, though this difference was not significant; **Table 2**) however, there were no statistically significant differences in serum Cr levels during the preoperative, post-operative, or the follow-up periods (**Table 2** and **Fig. 2**) in these patients.

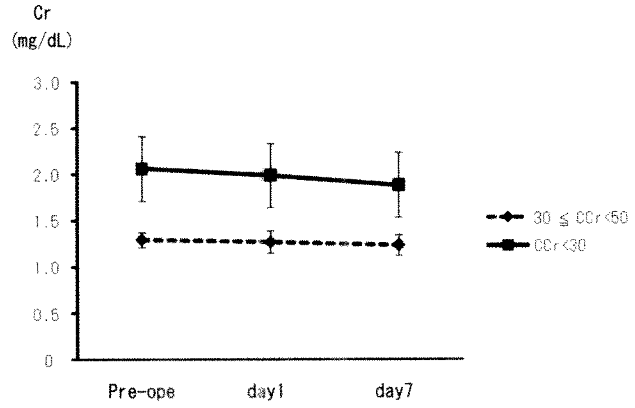

**Fig. 1** All patients had pre-existing chronic renal insufficiency with baseline CCr of 30 to 50 mL/min (group I) or less than 30 mL/min (group II). The absolute change in the serum creatinine level in each renal insufficiency group between the post-operative and preoperative time periods was similar between groups.

To reduce the cumulative nephrotoxic effects of intravascular contrast agents in patients with severe, chronic renal insufficiency, intravascular ultrasounds (Volcano

Table 2

| Factors | GroupA Suitable (N = 25) | GroupB Not suitable (N = 21) | P value |
|---|---|---|---|
| CCr(mL/min) | 38.1 | 33.8 | N.S. |
| Age(years) | 79.7 | 79.2 | N.S. |
| DM(%) | 28.0 | 4.8 | N.S. |
| AAA size(mm) | 53.1 | 58.0 | 0.03 |
| Operative time(min) | 153.4 | 163.4 | N.S. |
| Contrust agent(mL) | 101.6 | 93.1 | N.S. |
| Extension(numbers) | 0.7 | 1.5 | 0.02 |

Anatomical suitability for EVAR
aortic neck diameter of 18-28 mm, neck length ≥15 mm, neck angulation <60,
iliac diameter of 7.5-20 mm, length of iliac sealing zone ≥10 mm

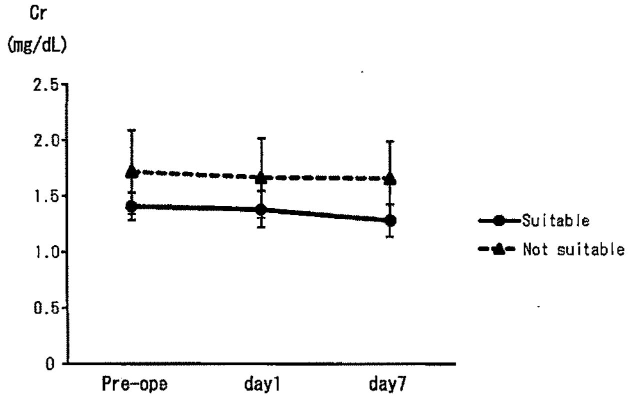

**Fig. 2** In group A, which were anatomically suitable for EVAR, the CCr tended to be higher in the preoperative period compared with the unsuitable group (group B), however, there were no statistically significant differences in serum creatinine levels observed during the preoperative, postoperative, or the follow-up periods.

s5 Imaging System) were used for 4 cases (of 46 cases: 8.7%), performing arteriography using only a minimal volume of contrast enhanced medium after the device is in place, near the level of the renal arteries; and not performing contrast-enhanced imaging studies after the operation. We have also performed color flow duplex ultrasound as the surveillance method post-EVAR to reduce the amount of contrast enhanced medium used in these patients.

None of the patients in our study required temporary or permanent hemodialysis during the follow-up period.

## DISCUSSION

Over the past decade, EVAR, which provides a less invasive alternative to open AAA repair, has become an established method for aortoiliac aneurysm repair.[1–6] EVAR requires intra-arterial administration of radiographic contrast enhanced mediums, which can cause impaired renal function, thus leading to end-stage renal disease. Chronic renal insufficiency is a relative contraindication to the use of intra-arterial contrast enhanced mediums and is thought to further increase the risks of EVAR.

Renal insufficiency is a well-recognized complication after open AAA repair; its incidence after EVAR remains poorly documented. The incidence of worsening renal function in patients undergoing open surgical AAA repair with normal preoperative renal function was found to be 5.4%, and increases two- to three-fold in patients with pre-existing chronic renal insufficiency.[15,16] Mortality with associated renal failure in patients undergoing EVAR with and without pre-existing chronic renal insufficiency has been reported to be 47% and 3%, respectively.[17] Acute renal failure requiring hemodialysis has been reported to complicate the course of 0.5% to 2% of patients undergoing elective AAA repair, with associated in-hospital mortality ranging from 25% to 66%.[15,18–26] Contrary to that report, our findings demonstrated that at 7 day after the operation, the incidence of a 10% or greater increase in serum Cr over the preoperative level was 10.9%, which was significantly lower in comparison to the previous report.

It was previously reported that chronic renal insufficiency increases the incidence of contrast-induced nephrotoxicity. High osmolar contrast agents, dehydration, nephrotoxic drugs, and diabetes mellitus further increase the risk for worsening renal failure. Nephropathy induced by contrast enhanced media is defined as an impairment in renal function that occurs within 48 to 72 hours of giving contrast enhanced medium. This impairment is characterized by an increase in serum Cr of at least 0.5 mg/dL, or 25% above the baseline. Cr typically peaks three to five days after contrast administration and returns to baseline values within two weeks. We focused a great deal of interest on the serum Cr at post-operative days 1, 2 and 7.

However, serum Cr is a poor indicator of renal function. The best measure of renal function—and, therefore, the risk of contrast nephropathy—is the glomerular filtration rate. The rate can be estimated from serum Cr using the Cockroft-Gault formula or by modification of diet in the renal disease formula. It is especially useful to estimate the GFR in patients with borderline serum Cr, a value of less than 60 mL/min predicts increased risk of contrast nephropathy.[7,27]

EVAR is usually possible if patients have appropriate anatomical morphology. Patients who are suitable for EVAR had been thought to have a reduced procedural length, decreased transfusion requirements and require lower amounts of contrast enhanced mediums. In our study, it was a most notable point that no statistically significant differences were found in the duration of surgery or the amount of contrast agents needed between the groups, despite additional devices needed for patients with inappropriate anatomical morphology for EVAR. Patients who were suitable for EVAR tended to indicate higher CCr in the preoperative period compared with patients who were not suitable for EVAR (not statistically significant), however, there were no statistically significant differences in serum Cr levels during the preoperative, post-operative, or the follow-up periods.

Our findings demonstrate that with perioperative precautions, including adequate intravenous hydration, use of low osmolar contrast agents, and avoidance of nephrotoxic drugs, the risk for worsening renal failure is low and not significantly increased in patients with pre-existing chronic renal insufficiency compared with patients with normal renal function. The incidence of post-operative complications between the study groups was not significantly different. In patients with chronic renal insufficiency who do not require dialysis, EVAR with intra-arterial contrast enhanced media can be performed with a limited and acceptable morbidity and mortality. With appropriate precautions, elevated Cr levels need not be a contraindication to the use of intra-arterial contrast enhanced mediums in EVAR. In addition, we have preferentially used duplex ultrasound imaging to evaluate maximum aneurysm diameter and presence of an endoleak in the follow-up period after EVAR.

Considering our results, the mean intraoperative contrast agent administration was 97.7 mL during EVAR, acceptable amounts of contrast enhanced mediums was about 100 mL for patients with pre-existing chronic renal insufficiency. However, in order to recommend precise tolerance level of contrast media in EVAR, further investigation in a larger number of patients is needed to assess the short-term and long-term results.

## CONCLUSION

Endovascular repair of abdominal aortic aneurysms in patients with pre-existing renal insufficiency can be performed safely with preservation of renal function, however, patients with pre-existing renal insufficiency continue to be at risk for progressive renal dysfunction, and protective measures should be taken to preserve renal function in this patient population. With appropriate precautions, including limiting the volume of nonionic contrast agents, chronic renal insufficiency, therefore, need not be a contraindication for EVAR with intra-arterial contrast agents, even if the patients did not have anatomical suitability for EVAR.

## DISCLOSURE STATEMENT

Atsushi Guntani and co-authors have no conflicts of interest.

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**Original Article**

# Early Outcomes of Open Abdominal Repair Versus Endovascular Repair for Abdominal Aortic Aneurysm: Report from National Hospital Organization Network Study in Japan

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National Hospital Organization Network Study Group in Japan for Abdominal Aortic Aneurysm

***Objective*: Early outcomes of open abdominal repair (OS) versus endovascular repair (EVAR) for abdominal aortic aneurysm were retrospectively analyzed, after commercialized devices for EVAR had become available in Japan.**

***Patients and Methods*: A total of 781 consecutive patients (OS, n = 522; EVAR, n = 259) were treated at ten medical centers between January 2008 and September 2010. The OS group comprised patients with preoperative shock (SOS, n = 34) and without shock (NOS, n = 488).**

***Results*: Patients in the EVAR group were 3 years older than those in the NOS group. There was greater prevalence of hostile abdomen, on dialysis, chronic obstructive pulmonary disease on inhaled drug, and cerebrovascular disease in the EVAR group than in the NOS group. Surgical mortality was 16 cases (2.0% in all patients, EVAR: 0.8%, NOS: 1.4%, SOS: 21%). Hospital stay >30 days was documented in 52 (11%) with NOS, 11 (33%) with SOS, and 8 (3%) with EVAR. Thirty late deaths included 6 aneurysm related death and 14 cardiovascular causes at a mean follow up of 1.0 year. The survival rates freedom from all cause death at one year, were 95 ± 1% in NOS and 94 ± 2% in EVAR respectively.**

***Conclusion*: Though significant differences in patient characteristics among three groups were noted, early results were satisfactory.**

***Keywords:*** abdominal aortic aneurysm, endovascular aneurysm repair, open surgical repair, multicenter cooperative study, less invasive approach

## INTRODUCTION

Since commercial devices to treat endovascular aneurysm repair (EVAR) for infra-renal abdominal aortic aneurysm (AAA) were approved for use in Japan in June 2007, both patients and physicians had acquired to choose appropriate treatment from two modalities, open surgical repair (OS) and EVAR. The relative advantage of each treatment strategy was disputed in Europe and North America including three prospective randomized trials.[1–6] However, there is no such trial conducted at the moment in Japanese population. In addition, contemporary

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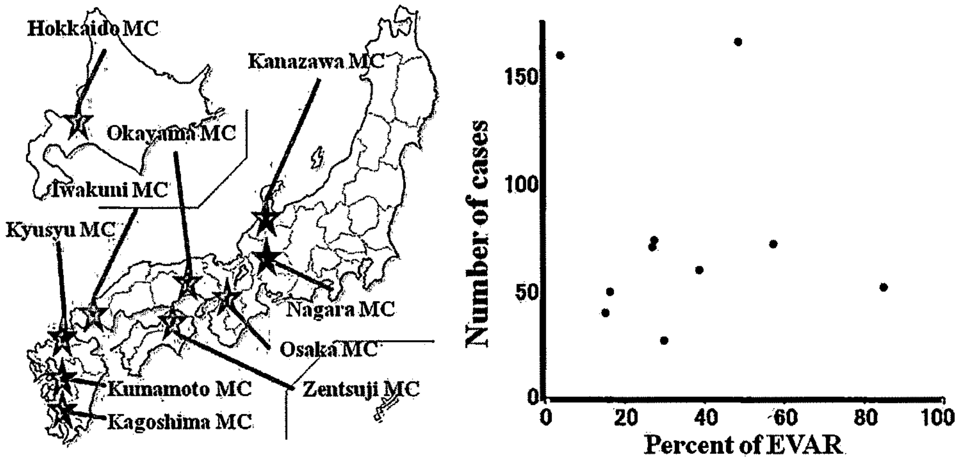

**Fig. 1** Location of ten medical centers of the National Hospital Organization on the left. Number of cases in each medical center and its ratio of EVAR to total cases. EVAR: endovascular aneurysmal repair

reports regarding open surgical repair of infra-renal AAA were scarce[7,8] after EVAR was introduced into Japan. A nationwide survey by the Japanese Society for Vascular Surgery provided valuable information over several years, though it is voluntarily collected and thus, potentially biased.[9] Ten medical centers of the National Hospital Organization (NHO) conducted a multicenter cooperative study to register AAA cases retrospectively. The interim goal of the present study was to report differences in patient backgrounds and preoperative surgical risks, as well as to compare treatment outcomes between two treatment modalities.

## METHODS

The study was conducted at 10 national medical centers participating NHO network study (**Fig. 1a**). It was a retrospective observational study to review and collect clinical data of AAA cases. All 10 databases were gathered to one large database of registration, which was analyzed. The study was approved by human rights ethical committee and the institutional review boards at each participating center. Progress of the study was assessed annually, and extension of the study was approved by central human rights ethical committee of NHO. All 10 participating institutions displayed the notice that they joined the NHO network study of AAA in the center according to the ethical guidelines for epidemiological research published by the Ministry of Education, Culture, Sports, Science and Technology, and the Ministry of Health, Labor and Welfare in Japan.[10] Patient registration Patient registration and management of the database were detailed elsewhere.[11] In brief, indications for treating AAA were as follows: maximum external diameter ≥ 5 cm or 4–5 cm with rapid enlargement, or saccular morphology, which carried a high risk of rupture. Some patients were treated for main location of common iliac artery aneurysm if their maximum size were more than twice the normal diameter. Each patient had a preoperative examination, including a multi-detector CT examination, according to the requirements of each participating center. The choice of treatment modality, EVAR or OS, depended upon the decision of surgeons and endovascular therapists (**Fig. 1b**). A total of 110 preoperative, intra-operative, and postoperative variables were collected. Parameters were selected, based on 10 risk scores previously published, for predicting risks of open abdominal repair of AAA.[12] After anonymization in a linkable fashion, all databases at 10 centers were connected into a large database at the Nagara Medical Center, which was shared by participants at ten NHO medical centers. From January 2008 through September 2010, a total of 786 patients were treated and registered. Of these patients, 5 had concomitant surgeries, such as coronary bypass surgery, or had scheduled surgery, which was not associated with AAA repair during the same hospitalization; thus, they were excluded from the present analysis. Accordingly, the study population was 781 patients. Of these, 259 patients underwent EVAR (EVAR group), and 522 patients had open surgical repair (OS group). In the OS group, 34 patients experienced preoperative shock due to a ruptured AAA and were treated emergently (SOS group), while the rest of 488 patients were treated electively without shock (NOS group).

**Table 1 Patient characteristics**

| | OS<br>n = 522 | SOS<br>n = 34 | NOS<br>n = 488 | EVAR<br>n = 259 | P value<br>(NOS vs EVAR) |
|---|---|---|---|---|---|
| Age | 74 ± 8 | 76 ± 9 | 74 ± 8 | 77 ± 7 | <0.001 |
| Age ≥80 year old # | 129 (25%) | 14 (41%) | 115 (24%) | 108 (42%) | <0.001 |
| Maximum diameter of aneurysm (mm) | 55 ± 12 | 68 ± 17 | 53 ± 11 | 51 ± 10 | <0.001 |
| Gender (male sex) | 418 (80%) | 23 (68%) | 395 (81%) | 216 (83%) | 0.3010 |
| BMI ≥30 | 8 (2%) | 1 (3%) | 7 (1%) | 6 (2%) | 0.3791 |
| BMI ≥25 | 138 (26%) | 8 (24%) | 130 (27%) | 65 (25%) | 0.5781 |
| Current smoker | 110 (21%) | 9 (26%) | 101 (21%) | 26 (10%) | 0.0005 |
| Ex-smoker | 216 (41%) | 11 (32%) | 205 (42%) | 116 (45%) | 0.2164 |
| Hypertension | 408 (78%) | 27 (79%) | 381 (78%) | 220 (85%) | 0.0031 |
| Diabetes mellitus | 63 (12%) | 3 (9%) | 60 (12%) | 45 (17%) | 0.0732 |
| On dialysis | 3 (0.6%) | 0 (0%) | 3 (0.6%) | 6 (2%) | 0.0476 |
| Preoperative renal dysfunction (Cr ≥1.5) without dialysis | 58 (11%) | 9 (26%) | 49 (10%) | 18 (7%) | 0.7632 |
| Liver chirrohsis | 4 (1.5%) | 0 (0%) | 4 (0.8%) | 4 (0.7%) | 0.8637 |
| Coronary artery disease | 169 (32%) | 3 (9%) | 166 (34%) | 86 (33%) | 0.6459 |
| Myocardial ischemia | 95 (18%) | 2 (6%) | 93 (19%) | 50 (19%) | 0.1503 |
| Stroke | 88 (17%) | 6 (18%) | 82 (17%) | 72 (28%) | 0.0005 |
| with residual neurological deficit | 23 (4%) | 3 (9%) | 20 (4%) | 18 (7%) | |
| without neurological deficit | 65 (12%) | 3 (9%) | 62 (13%) | 54 (21%) | |
| NYHA class II | 33 (6%) | 5 (15%) | 28 (6%) | 43 (17%) | 0.1500 |
| NYHA class III | 3 (0.6%) | 2 (6%) | 1 (0.2%) | 8 (3%) | |
| NYHA class IV | 1 (0.2% | 0 (0%) | 1 (0.2%) | 0 (0%) | |
| Previous PPI | 2 (0.4%) | 0 (0%) | 2 (0.4%) | 8 (3%) | 0.3463 |
| Preoperative steroid use | 16 (3%) | 3 (9%) | 13 (3%) | 9 (3%) | 0.5428 |
| COPD on inhaled drug therapy | 6 (1%) | 1 (3%) | 5 (1%) | 17 (7%) | <0.001 |
| FEV1.0% <70% | —— | —— | 104 (20%) | 60 (23%) | 0.7419 |
| Preoperative VC (<70% of normal) | —— | —— | 47 (9%) | 16 (6%) | 0.1771 |
| History of abdominal surgery | 79 (15%) | 6 (18%) | 73 (15%) | 64 (25%) | 0.0012 |
| Once | 67 (13%) | 5 (15%) | 62 (13%) | 47 (18%) | 0.0505 |
| Twice or more | 12 (2%) | 1 (3%) | 11 (2%) | 17 (7%) | 0.0044 |

OS: open surgery; SOS: open surgery with preoperative shock; NOS: open surgery without preoperative shock; PPI: permanent pacemaker implantation

## Outcome measures

The primary outcome measure was surgical mortality. It is defined as either any cause of death within 30 days after operation or in-hospital mortality without discharge at any time. The secondary outcome measures included early morbidities, and intermediate term results. Details of treatments were procedure time, volume of blood transfusion, and process of recovery, including hours of respiratory management, length of intensive care unit stay (ICU stay), procedure failure requiring additional procedure during the same hospitalization, and re-admission within 30 days. Preoperative patient characteristics and intra-operative and postoperative factors are described in **Table 1**.

## Statistical analysis

Statistical analysis of the intergroup comparison was conducted mainly between the EVAR group and NOS

**Table 2 Procedure related factors and postoperative recovery**

| | OS<br>n = 522 | SOS<br>n = 34 | NOS<br>n = 488 | EVAR<br>n = 259 | P value<br>(NOS vs EVAR) |
|---|---|---|---|---|---|
| Procedure time (min.) | 234 ± 85 | 235 ± 100 | 234 ± 84 | 161 ± 61 | <0.0001 |
| Red blood cell transfusion (ml) | 868 ± 1126 | 3073 ± 2353 | 724 ± 807 | 170 ± 370 | <0.0001 |
| Respiratory Management (hours) | 33.2 ± 64.7 | 6.8 ± 34.7 | 4.8 ± 30.4 | 0.3 ± 1.2 | 0.0303 |
| Hospital stay after treatment (days) | 21.4 ± 23.9 | 28 ± 29 | 18 ± 21 | 10.0 ± 8.9 | <0.0001 |
| Duration until walking (days) | 3.8 ± 5.3 | 9.9 ± 17.0 | 2.9 ± 4.5 | 1.1 ± 0.8 | <0.0001 |
| Duration until eating meal (days) | 3.8 ± 2.4 | 5.1 ± 2.4 | 2.9 ± 4.5 | 1.2 ± 2.1 | <0.0001 |
| Hospitalization at 30 days after treatment | 70 | 11 | 59 | 16 | 0.0113 |
| Prolonged hospital stay (>30days) | 63 | 11 | 52 | 8 | <0.0001 |
| Readmission within 30 days | 7 | 0 | 7 | 8 | 0.1488 |

OS: open surgery; SOS: open surgery with preoperative shock; NOS: open surgery without preoperative shock

group because no patients had EVAR under preoperative shock state in the present study population. Statistical software package, JMP version 8 (SAS, Institute Japan, Tokyo) was used for statistical analysis. The characteristics of the patients between two treatment modality were compared by using chi-square tests for categorical variables and t-tests for continuous variables. Survival proportion rates freedom from all cause death, cardiovascular death, aneurysm related death and other events were estimated with the use of Kaplan–Meier method, and comparisons were made with the use of log-rank analysis. P values of less than 0.05 were considered to indicate statistical significance.

## RESULTS

### Patient characteristics and preoperative condition

Patient characteristics are detailed in **Table 1**. Patients who underwent EVAR were significantly older than those in NOS group (P <0.001), while patients in SOS were almost same age compared with those in EVAR. Approximately 42% of patients were 80 years old or older in EVAR group, while 24% in NOS group. Maximum diameter of AAA size is shown in **Table 1**, as well. Mean diameter was significantly smaller in the EVAR than in the NOS group (51 ± 10 mm vs 55 ± 12 mm). It was noted that patients who were currently smoking were less prevalent in the EVAR group than in the NOS group (21% vs 10%). It was realized as well that the following risk factors were more prevalent in EVAR group than NOS group: on dialysis, previous history of stroke, history of abdominal surgery and chronic obstructive lung disease (COPD) on inhaled drug.

### Treatments and postoperative recovery

Devices used for EVAR were as follows: COOK Zenith AAA endoprosthesis in 127 cases (49%), Gore Tex Excluder in 111 cases (43%), and Endologix PowerLink in 19 cases (7%). Eighty-nine patients (34%) who had EVAR were for the case beyond the manufacturer's Instructions for Use (IFU). With respect to procedure-related factors, results are shown in **Table 2**. NOS group required a longer procedure time, increased blood transfusion, and longer respiratory management. Recovery from the procedure, such as duration until walking and duration to resume meal, was faster in the EVAR group than in the NOS group. As a result, a long hospital stay, defined as >30 days, was significantly reduced in the EVAR group than in the NOS group.

### Early results

Early mortality and morbidity are detailed in **Table 3.** In-hospital mortality was 16 cases (2.0% in all patients, EVAR: 0.8%, NOS: 1.4%, SOS: 21%). Early morbidity included delayed wound healing or infection (n = 14), deterioration of renal dysfunction (n = 34), stroke (n = 3), gastrointestinal complications (n = 34), and peripheral thromboembolism (n = 10) congestive heart failure (n = 8), prolonged ventilation (>72 hours, n = 9). It was noted that postoperative stroke was more frequent in the EVAR group, while gastrointestinal complications were more common in the NOS group. Unexpectedly, deterioration of renal dysfunction either a new event from dialysis or a twofold rise in the creatinine level was more frequent in the NOS group than in the EVAR group. Hospital stays >30 days was

**Table 3 Early mortality and morbidity**

| | OS<br>n = 522 | SOS<br>n = 34 | NOS<br>n = 488 | EVAR<br>n = 259 | P value<br>(NOS vs EVAR) |
|---|---|---|---|---|---|
| Operative mortality | 14 (2.7%) | 7 (21%) | 7 (1.4%) | 2 (0.8%) | 0.3095 |
| Endoleak | | | | 70 (27%) | |
| Type I | | | | 9 | |
| Type II | | | | 52 | |
| Type III | | | | 4 | |
| Type IV | | | | 5 | |
| EVAR leg occlusion or stenosis | | | | 3 (1%) | |
| Delayed wound healing/ infection | 14 (3%) | 0 (0%) | 14 (3%) | 7 (3%) | 0.8960 |
| Stroke | 0 (0%) | 0 (0%) | 0 (0%) | 3 (1%) | 0.0172 |
| Perioperative myocardial infarction | 3 (0.6%) | 0 (0%) | 3 (0.6%) | 0 (0%) | 0.2061 |
| Congestive Heart failure | 8 (2%) | 1 (3%) | 7 (1%) | 0 (0%) | 0.0528 |
| Intervention for arrhythmia | 6 (1%) | 2 (6%) | 4 (0.8%) | 0 (0%) | 0.1440 |
| Dialysis (postoperative new event) | 6 (1%) | 1 (3%) | 5 (1%) | 2 (0.8%) | 0.7333 |
| Deterioration of renal function | 34 (7%) | 5 (15%) | 29 (6%) | 4 (2%) | 0.0054 |
| Prolonged respiratory management | 9 (2%) | 3 (9%) | 6 (1%) | 0 (0%) | 0.0732 |
| Thorachiostomy | 4 (0.8%) | 1 (3%) | 3 (0.6%) | 0 (0%) | 0.2061 |
| Peripheral vascular malperfusion | 10 (2%) | 2 (6%) | 8 (2%) | 5 (2%) | 0.7721 |
| Postoperative liver dysfunction | 6 (1%) | 4 (12%) | 2 (0.4%) | 1 (0.4%) | 0.9611 |
| Multiple organ failure | 6 (1%) | 2 (6%) | 4 (0.8%) | 1 (0.4%) | 0.4891 |
| Gastrointestinal complication | 34 (7%) | 9 (26%) | 25 (5%) | 4 (2%) | 0.0160 |
| Postoperative pneumonia | 4 (0.8%) | 1 (3%) | 3 (0.6%) | 0 (0%) | 0.2061 |
| Deep vein thrombosis | 2 (0.4%) | 0 (0%) | 2 (0.4%) | 0 (0%) | 0.3022 |
| Prosthetic graft infection | 2 (0.4%) | 1 (3%) | 1 (0.2%) | 0 (0%) | 0.4660 |
| Allergic reaction to contrast medium | 0 (0%) | 0 (0%) | 0 (0%) | 1 (0.4%) | 0.1696 |
| Secondary procedure before dismissal | | | | | |
| Management for endoleaks | ––– | ––– | ––– | 3 | |
| Intervention for leg ischemia | 10 | 1 | 9 | 5 | 0.9341 |
| Delayed wound closure or repair | 4 | 3 | 1 | 1 | 0.6483 |
| Ileus/gastrointestinal complication | 4 | 0 | 4 | 0 | 0.1440 |

Operative death is defined as death within 30 days or death during index hospitalization.
OS: open surgery; SOS: open surgery with preoperative shock; NOS: open surgery without preoperative shock
Deterioration of renal dysfunction is defined as that highest postoperative creatinine level was higher than the twofold of preoperative creatinin level.

52 patients (11%) in the NOS group, 11 (33%) in the SOS and 8 (3%) in the EVAR. In the EVAR group, endoleaks were observed at the end of the procedure in 70 (27%) patients (type I, n = 9; type II, n = 52; type III, n = 4; type IV, n = 5). The secondary procedure performed during index hospitalization is summarized in **Table 3**, as well. Interventions for postoperative leg ischemia were required in 15 patients (2 in SOS group, 8 in NOS group, 5 in EVAR group). With respect to readmission within 30 days, 15 patients (7 in NOS and 8 in EVAR) were readmitted. Causes of readmission within 30 days after EVAR were, in 2 patients, late intervention for type I endoleaks, and in 1 patient each, a wound problem, allergic reaction to follow-up CT at the outpatient clinic, urinary tract infection, new type B dissection, surgery for colon cancer, and deterioration of concomitant interstitial pneumonia.. Causes of readmission within 30 days after open surgery were, in 2 patients, wound infection and in 1 patient each, surgery for colon cancer, ileus, graft infection, surgery for peripheral arterial disease and cerebral bleeding

## Intermediate term results

Mean duration of follow-up was only 1.0 ± 0.8 years.

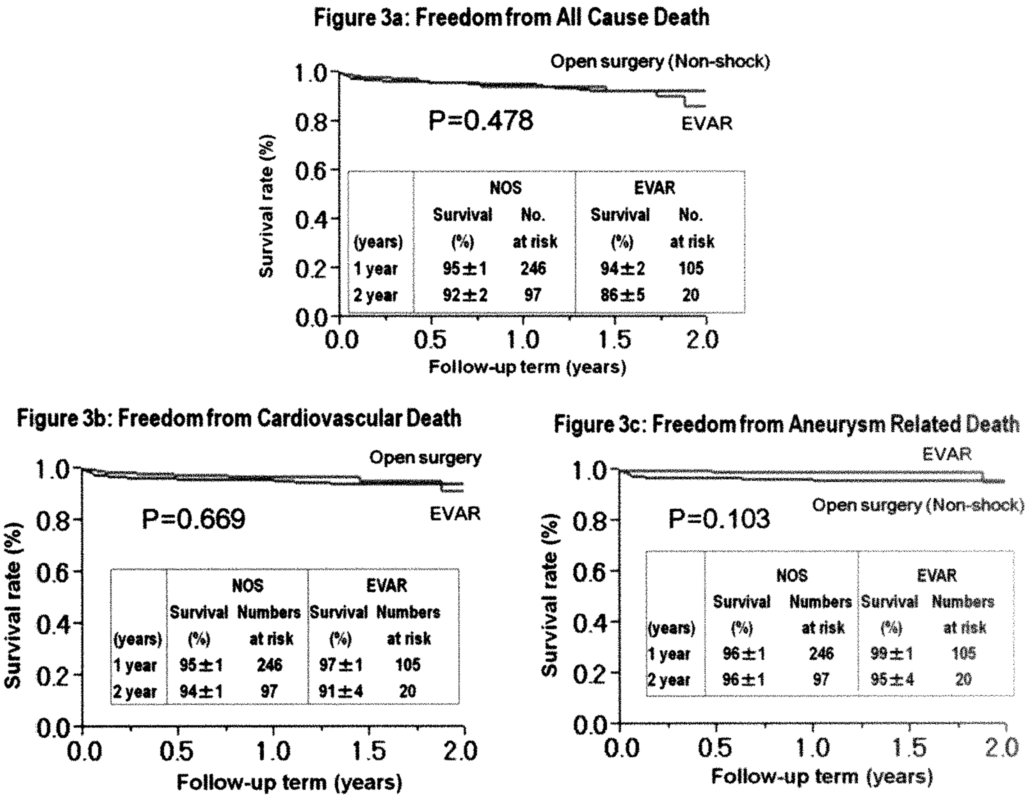
Figure 3a: Freedom from All Cause Death

| (years) | NOS Survival (%) | NOS No. at risk | EVAR Survival (%) | EVAR No. at risk |
|---|---|---|---|---|
| 1 year | 95±1 | 246 | 94±2 | 105 |
| 2 year | 92±2 | 97 | 86±5 | 20 |

Figure 3b: Freedom from Cardiovascular Death

| (years) | NOS Survival (%) | NOS Numbers at risk | EVAR Survival (%) | EVAR Numbers at risk |
|---|---|---|---|---|
| 1 year | 95±1 | 246 | 97±1 | 105 |
| 2 year | 94±1 | 97 | 91±4 | 20 |

Figure 3c: Freedom from Aneurysm Related Death

| (years) | NOS Survival (%) | NOS Numbers at risk | EVAR Survival (%) | EVAR Numbers at risk |
|---|---|---|---|---|
| 1 year | 96±1 | 246 | 99±1 | 105 |
| 2 year | 96±1 | 97 | 95±4 | 20 |

**Fig. 2** Kaplan-Meier survival analyses freedom from events.
**a**: Survival curve freedom from all-cause death.
**b**: Survival curve freedom from cardiovascular death.
**c**: Survival curve freedom from aneurysm-related death.

Twenty-four patients died during the follow-up term. One patient in the NOS group died of prosthetic graft infection. Five patients (3 in NOS group and 2 in EVAR group) died of unknown causes. These 6 patients were considered as aneurysm related death. Additional 14 patients died of cardiovascular causes, which were not directly related to the AAA and its repair. Kaplan Meier survival analysis freedom from all cause death showed good 1 year survival rates of 95% for NOS patients and 94% for EVAR patients (**Fig. 2a**). Survival rates freedom from cardiovascular death and aneurysm-related death at one year were 95% and 96% for the NOS group and 97% and 99% for the EVAR group at one year (**Fig. 2b** and **2c**).

## Discussion

The present results of this multicenter cooperative study regarding AAA repair provides contemporary surgical outcomes of open abdominal repair as well as initial results of EVAR after it was introduced into Japan. First of all, it is clearly recognized that surgical mortalities of 0.8% in EVAR group, 1.4% in NOS group and 21% in SOS group were all satisfactory. Early mortality for elective AAA repair was reported as 1.6%–4.7% with open abdominal repair and 0.5%–1.7% with EVAR.[1–6] Our results are equivalent to or even better than these results. In the current study, it may be inappropriate to compare these 2 groups because the study is a retrospective observational study and patient characteristics and background were significantly different between them. It was also suggested that the vascular surgeon or endovasculartherapist selected the treatment modality for each patient, according to their institutionalized criterion or preference. In fact, some institutions treated most patients with open surgery, while others did so with EVAR (**Fig. 1b**). The multicenter database, however, revealed that patients in the EVAR group were three years older than those in the NOS group, on average. They were also characterized with a greater prevalence of history of stroke, previous abdominal surgery, on dialysis and COPD on inhaled drug.

Secondly, regarding patients in the SOS group, a small number of patients that had an episode of preoperative shock without rupture might have been included in the group. However, most patients in the group were referred to as having a ruptured AAA and were treated only with open abdominal repair in the present study population. Recently, surgical management of ruptured AAA was systematically reviewed and was discussed elsewhere, based on the reports, mainly from Europe and USA.[13,14] In the review, the 30-day mortality rate of open abdominal repair in this subset of patients ranged from 13.6% to 75%, mostly between 20% and 50%.[13] The large study of a cooperative multicenter cohort study comprising 49 institutions in 13 countries compared EVAR with open abdominal repair for ruptured AAA, reporting 30-day mortality of 19.7% in patients treated with EVAR compared with 36.3% in those with open abdominal surgery.[14] However, it was pointed out as well that there was selection bias as patients who had EVAR were hemodynamically stable enough to select it as a treatment strategy with radiological evaluation by CT scan.[13,14] Although emergent EVAR for ruptured AAA was widely applied with excellent results in U.S. and European countries, no such cases were reported and registered from NHO medical centers at present.

Third, several interesting observations were realized in the study results. Factors associated with the procedure or surgery demonstrated that patients in the EVAR group recovered earlier than those in the NOS group, resulting in a significant reduction in the duration of hospital stay. Patients who were hospitalized for more than 30 days were more frequently observed in the NOS group than in the EVAR group. With respect to early morbidity, as anticipated, incidence of stroke was more common in the EVAR group, while gastrointestinal complication was in the NOS group. Increased incidence of stroke might have been related with increased prevalence of preoperative history of stroke. However, in order to reduce it, manipulations of wire and catheter around ascending aorta or aortic arch should be gentle and cautious. Preoperative assessment of atheroma by CT is helpful. Unexpectedly deterioration of renal dysfunction was more frequent in the NOS group than in EVAR group, though contrast medium was inevitably used in the EVAR group. Preoperative renal dysfunction has been considered as a relative contraindication for EVAR. The results of the present study, however, suggest that EVAR is the choice of treatment rather than open surgical repair in patients with mild to moderate renal dysfunction if treatment for AAA is unavoidable. A comparison between groups in a well-controlled manner will be required to have conclusion in this subset of patients.

Fourth, the present report must be the first one of multicenter cooperative study consisting of a consecutive series of patients having open surgical repair of AAA for Japanese population. The clinical studies regarding a large number of open surgical repair of AAA were reported from England, U.S. and other countries.[1–6,12] However, no English literature of such study for Japanese population was found within our investigation. It was only available that the nationwide survey by Japanese Society for Vascular Surgery.[9] It provided extremely valuable information in Japanese population that the surgical mortality of elective AAA repair ranged form 0.6% to 0.9% over several years.[9] However, it must be taken into account as well that data were collected on voluntarily fashion by yearly questionnaire so that it was potentially biased. Single institutional reports of a consecutive series over several years were available recently in Japan. The Kurume University was congratulated to report no mortality for elective open abdominal repair of AAA over 6 years of their experience.[7] Their experience included 13% of patients over 80 years of age[7] The other literature from Nagoya University reported 2.2% of in-hospital mortality in patients with elective open surgical repair of infra-renal or juxta-renal AAA over 6 years.[8] As institutions of NHO AAA study group were typical regional medical centers in Japan, it is supposed that the results of the present study must be representative data in Japanese population. With respect to early results in EVAR, The Japanese Committee for Stentgraft Management (JACSM) reported its successful role of introducing EVAR into Japan safely and early mortality of 0.4% in the first two years.[15]

Finally with respect to late mortality, follow-up term was limited as 1.0 years on average at present. Therefore, meaningful interpretation was not elucidated. Under the limited follow-up term at present, survival rates freedom from all cause death, cardiovascular death and aneurysm related death were satisfactory in both group. However, five out of six patients who died of unknown causes were considered to be aneurysm-related deaths, according to the reporting standard of the cardiovascular society. Real causes might have been cardiovascular or non-cardiovascular, which may change the interpretation of follow-up data between groups. In addition, late morbidity has not been collected sufficiently, so far. Only cases of readmission within 30 days were completed in the present study, which included two late interventions for type I endoleaks in EVAR. It is absolutely required to collect information on late morbidity and secondary interventions during follow-up.

### Limitation of the study

The present interim report had many limitations. It is obvious that the report was based on data collected retrospectively. The NOS and EVAR groups were not comparable, in terms of patient background and characteristics, as well as anatomy of the aneurysm. The follow-up term was short and insufficient. Longer follow-up and further accumulation of registered cases are mandatory. In particular, late morbidity and secondary intervention at follow up need to be collected.

## CONCLUSION

The present multicenter, cooperative study provides contemporary outcomes of AAA repair, either open abdominal repair or endovascular repair, in Japan. Although the process of selecting the treatment modality was different in each medical center, early outcomes were satisfactory, overall.

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**Original Article**

# Lowered LDL-C Levels Reduce Later Local Vascular Events after Surgical or Endovascular Treatment of Peripheral Artery Disease

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***Purpose:*** **To examine the relationship between incidence of later, local vascular events (restenosis and occlusion) and clinical factors including lipid levels after surgical or endovascular treatment of peripheral artery disease (PAD).**

***Methods:*** **Consecutive 418 PAD lesions (in 308 patients under the age of 70) treated with surgical (n = 188) or endovascular (n = 230) repair for iliac (n = 228) and infrainguinal (n = 190) lesions were retrospectively analyzed. Clinical features and lipid levels were compared between patients who developed vascular events (n = 51; VE group) and those who did not (n = 257; NoVE group).**

***Results:*** **Among assessed factors, post-therapeutic low-density lipoprotein cholesterol (LDL-C) levels (mg/dL) were significantly higher in the VE group (120.4 ± 31.2) than in the NoVE group (108.2 ± 25.1) (*P* = 0.01). Infrainguinal lesions were more common in the VE than in the NoVE group (*P* <0.001). Cox hazard analysis indicated that infrainguinal lesions relative to iliac lesions significantly increased the risk of vascular events (hazard ratio (HR) 3.35; 95% CI 1.63–6.90; *P* = 0.001) and post-therapeutic LDL-C levels <130 (mg/dL) decreased the risk (HR 0.34; 95%CI 0.17–0.67; *P* = 0.002).**

***Conclusion:*** **Lowered post-therapeutic LDL-C levels can decrease the risk of later, local vascular events after PAD treatment. These results may support the rationale for aggressive lipid-modifying therapy for PAD.**

***Keywords:*** dyslipidemia, LDL-C, PAD, endovascular treatment, surgical treatment

## INTRODUCTION

Peripheral artery disease (PAD) due to atherosclerosis occurs commonly, with an estimated prevalence as high as 21% in patients aged over 65 years in the Western world.[1–4] Symptoms of PAD range from claudication to rest pain or tissue loss, and patients presenting with chronic critical limb ischemia (CLI) are frequently associated with other arteriosclerotic cardiovascular disorders like coronary artery disease (CAD).[2,3,5] Thus, reductions in atherosclerotic risk factors, such as smoking cessation, treatment for diabetes and dyslipidemia, play an important role in the treatment of PAD as well as treatment for affected arteries.[6,7] The established American Heart Association guidelines recommend the use of hydroxymethylglutaryl (HMG) coenzyme-A reductase inhibitors (statin drugs), angiotensin converting enzyme (ACE) inhibitors, and antiplatelet agents in patients with systemic atherosclerosis, such as those undergoing operative intervention to treat PAD.[6–8]

Currently, most patients with PAD are treated on the

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basis of the Trans-Atlantic Inter-Society Consensus document on Management of Peripheral Arterial Disease (TASC) and the Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II) Steering Committee guidelines.[9,10] Long-term results after treatment of PAD, however, may vary with the type and extent of the lesions and the presence of atherosclerotic risk factors and comorbidity. The reported predictors for adverse outcomes after treatment of PAD include the TASC type C/type D lesions, stenosis of the ipsilateral peripheral artery, smoking history, diabetes mellitus (DM), chronic renal failure with hemodialysis, and critical limb ischemia.[6,11,12] With regard to serum lipid levels, few reports have described the direct relationship between the lipid levels and long-term results of the affected arteries after surgical or endovascular treatment of PAD.[6,13] Although the relative benefit of lipid-modifying therapies for claudication symptoms remains unclear,[6] the hypothesis that lowered low-density lipoprotein cholesterol (LDL-C) levels are beneficial in promoting graft patency in surgically treated cases and decreasing local vascular events (restenosis and occlusion) in patients with PAD is logical. It seems to be important to clarify the direct relationship between the lipid levels such as LDL-C and high-density lipoprotein cholesterol (HDL-C) and long-term local vascular events after surgical or endovascular treatment of PAD, as a background rationale for aggressive lipid-modifying therapy. For that purpose, we retrospectively analyzed the pre- and post-therapeutic serum lipid levels and other atherosclerotic risk factors in patients undergoing surgical bypass procedures or endovascular treatment (EVT) for PAD. The purpose of this study was to investigate the relationship between the incidence of later local vascular events (restenosis and occlusion) and clinical factors including lipid levels after surgical or endovascular treatment for PAD.

## PATIENTS AND METHODS

This retrospective study was performed on consecutive 418 PAD lesions of the lower extremity treated with surgical procedures (n = 188) or EVT (n = 230) in 308 patients under the age of 70, between April 1989 and November 2010 in the Division of Cardiovascular Surgery, Aishin Memorial Hospital. All patients were Japanese and consisted of 270 male and 38 female patients with a mean age of 62.3 ± 6.0 years (range from 50 to 69 years). Clinical symptoms of these patients included intermittent claudication (IC) for 260 (84.4%) and CLI for 48 patients (15.6%). Patients with IC were considered for surgical procedures or EVT in principle when medical therapies failed to significantly improve ischemic symptoms. The diagnosis of PAD was established by the findings of digital subtraction angiography (DSA) or computed tomographic angiography (CTA) in all patients, and arterial segments with greater than 75% diameter stenosis were determined as significant stenosis. Either before or after revascularization, 217 patients (70.5%) received treatment for hypertension (HTN); 124 (40.3%) for DM and 119 (38.6%) received statin drugs for dyslipidemia. Of the 119 patients who received statin, 49 patients received statin drugs since before the treatment of PAD, and all 119 patients received after the treatment. Nineteen patients (6.2%) needed hemodialysis due to chronic renal failure. Antiplatelet therapy or anticoagulant agents were given in principle to all patients, unless the patient presented with serious side effects. Due to the high annual mortality rate reported in patients with PAD, ranging from 4% to 6% and even as high as 25% in patients presenting with CLI,[6] study subjects were limited to those under the age of 70 at treatment to ensure sufficient period of follow-up and to minimize the influence of aging on the local vascular events.

Of 418 lesions investigated in this study, there were 228 iliac lesions and 190 infrainguinal lesions. The iliac lesions included TASC II type A for 123, type B for 45, type C for 13, and type D for 47 lesions, and the infrainguinal lesions included TASC II type A for 53, type B for 10, type C for 97, and type D for 30 lesions.[9,10] Of these, 188 lesions were treated with surgery, including TASC II type B for 11, type C for 109, and type D for 68 lesions, and 230 lesions were treated with EVT, including TASC II type A for 176, type B for 44, type C for 1, and type D for 9 lesions. Therapeutic strategy during the study period has been changed in response to progress in endovascular technology and publication of TASC and TASC II guidelines.[9,10] Before the Palmaz stent was available in the EVT, surgical procedures tended to be selected more often, mainly due to a relatively high incidence of restenosis occurrence after plain old balloon angioplasty (POBA). Since the publication of TASC II guidelines, most of TASC II type A and type B lesions in the iliac arteries have been treated with EVT and the number of patients undergoing infrainguinal surgical bypass has been diminished.

Among 188 lesions treated with open surgical procedures, prosthetic graft (Dacron or expanded polytetrafluoroethylene (ePTFE) graft) was used in 176 lesion and autologous saphenous vein graft in 12 lesions. In these lesions, the etiologic source of PAD was considered to be atherosclerosis in all cases. Around the same time as study period, there were 5 patients who developed an early graft failure within a month after surgery and one patient who died within a month. These patients were not included in this study, as the main purpose of this study was to evaluate long-term effects of lipid levels on local vascular events. Among 230 lesions treated with EVT, 149 lesions were treated concomitantly with stent placement (Palmaz stent for 68 lesions and nitinol shape-memory alloy-recoverable technology (SMART) stent for 81 lesions) and other 81 lesions were treated with POBA without stent placement.

Follow-up of the patient after discharge has been conducted periodically in principle at the outpatient clinic in our institute. Blood pressure at the outpatient clinic over the course of follow-up was controlled with a target systolic pressure of less than 140 mmHg and diastolic pressure of less than 90 mmHg. Patients with HTN received ACE inhibitors or angiotensin-II receptor blockers concurrently with additional oral calcium-channel blockers as appropriate. For the measurement of serum lipid levels, blood samples for biochemical assay were collected after an overnight fast, and the serum was analyzed for total cholesterol (TC), HDL-C, and triglycerides (TG) using automated assay. The LDL-C levels were calculated by Friedewald formula. The LDL-C levels during the follow-up period were in principle controlled with a target value of at least less than 130 mg/dL using statin drugs and/or fibrates on physician preference. Post-therapeutic lipid levels in patients were determined by the mean value of laboratory data obtained at least 3 months after surgical treatment or EVT. Patients who were referred to other hospitals or lost to follow-up within 3 months after discharge were not included in this study. During the study period, there were 29 patients under such conditions, most of whom were referred to their family doctor at a long distance on a good postoperative course. Two patients, however, were transferred due to cerebral infarction.

Local vascular events, defined as restenosis greater than 75% in diameter and occlusion in this study, was suspected by the recurrence of ischemic symptoms of the lower extremity or a significant decrease of 20% or more in ankle brachial index (ABI) compared to the previous levels and confirmed by DSA or CTA. Duplex ultrasound, which is a useful tool to provide graft surveillance after infrainguinal bypass with saphenous venous (but not prosthetic) conduit,[6] had not been used as routine surveillance in this study, as the prosthetic graft was used in the majority of patients undergoing surgical procedures. Clinical features including the age and gender, atherosclerotic risk factors, and pre-therapeutic and post-therapeutic lipid levels were recorded and compared between the patients who developed later local vascular events (n = 51; VE group) and those who did not develop events (n = 257; NoVE group). The clinical factors that may be related to the development of later vascular events were subjected to multivariate analysis to identify correlations with the later events occurrence. Kaplan-Meier method was used to evaluate the rate of freedom from local vascular events. The endpoint of this study was defined as the time at local vascular events or tissue loss occurrence, the time of death from any cause (regarded as censored case), or time at the end of follow-up for a maximum of 10 years. In patients with multiple local vascular events, the time at the first event was defined as the endpoint of the study. This study was approved by the Hospital Ethics Committee and all patients received a full explanation of surgical or endovascular treatment and related risks, and treatment strategy for the vascular lesions by physicians. The mean follow-up period until the endpoint of the study was 51.8 ± 38.3 (months) after surgical treatment of EVT for PAD.

## STATISTICAL ANALYSIS

Descriptive statistics were used, and continuous variables are presented as the mean ± standard deviation (SD) and compared using the Student's t-test for parametric and Mann-Whitney U-test for non-parametric analyses. Chi-square test was used for comparisons of categorical variables. The rate of freedom from local vascular events (VE-free rate) was calculated by the Kaplan-Meier method and comparisons between the two groups were performed by the logrank test. Cox proportional hazard model was applied to determine the effects of variables over time on local vascular events during the follow-up period. Differences were statistically considered significant at $P < 0.05$. All statistical analysis was performed using Dr. SPSS II version 11.0.1 J (SPSS Inc., Chicago, Illinois).

## RESULTS

Overview of the clinical characteristics and atherosclerotic risk factors compared between the VE and NoVE group is summarized in **Table 1**. Later local vascular

**Table 1 Comparative studies between the patients who did and did not develop later vascular events**

| | Total (n = 308) | Vascular events (+) (VE group; n = 51) | Vascular events (−) (NoVE group; n = 257) | *P* value |
|---|---|---|---|---|
| Age (year) | 62.3 ± 6.0 | 62.8 ± 5.4 | 62.2 ± 6.1 | 0.533 |
| Male/Female | 270/38 | 42/9 | 228/29 | 0.207 |
| HTN treatment (%) | 217 (70.5%) | 35 (68.6%) | 182 (70.8%) | 0.740 |
| DM treatment (%) | 124 (40.3%) | 25 (49.0%) | 99 (38.5%) | 0.211 |
| Statin drugs (%) | 119 (38.6%) | 21 (26.3%) | 98 (13.4%) | 0.753 |
| PCI or CABG (%) | 30 (9.7%) | 2 (3.9%) | 28 (10.9%) | 0.193 |
| Hemodyalysis (%) | 19 (6.2%) | 4 (7.8%) | 15 (5.8%) | 0.532 |
| Pre-therapeutic lipid levels | | | | |
| HDL-C (mg/dL) | 43.6 ± 13.0 | 43.5 ± 10.5 | 43.6 ± 13.5 | 0.940 |
| LDL-C (mg/dL) | 116.1 ± 30.7 | 119.2 ± 36.4 | 115.5 ± 29.5 | 0.439 |
| LDL-C/HDL-C ratio | 2.90 ± 1.17 | 2.89 ± 1.05 | 2.91 ± 1.19 | 0.898 |
| TG (mg/dL) | 139.3 ± 72.7 | 149.6 ± 94.1 | 137.3 ± 67.7 | 0.270 |
| Post-therapeutic lipid levels | | | | |
| HDL-C (mg/dL) | 49.1 ± 13.9 | 50.7 ± 14.2 | 48.9 ± 13.8 | 0.473 |
| LDL-C (mg/dL) | 109.9 ± 26.2 | 120.4 ± 31.2 | 108.2 ± 25.1 | 0.011 |
| LDL-C/HDL-C | 2.45 ± 0.89 | 2.56 ± 0.88 | 2.43 ± 0.90 | 0.446 |
| TG (mg/dL) | 140.3 ± 62.5 | 142.5 ± 62.8 | 139.9 ± 62.6 | 0.821 |
| Follow up period (months) | 51.8 ± 38.3 | 32.9 ± 28.8 | 55.5 ± 38.9 | <0.001 |
| Treated lesions | (n = 418) | (n = 60) | (n = 358) | |
| Iliac artery | 228 (54.5%) | 19 (31.7%) | 209 (58.4%) | |
| Femoral artery | 165 (39.5%) | 37 (61.7%) | 128 (35.8%) | <0.001 |
| Popliteal artery or below | 25 ( 6.0%) | 4 ( 6.7%) | 21 ( 5.9%) | |
| The type of lesion | | | | |
| TASC II type A or B | 231 (55.3%) | 25 (41.7%) | 206 (57.5%) | |
| TASC II type C or D | 187 (44.7%) | 35 (58.3%) | 152 (42.4%) | 0.025 |
| Treatment for vascular lesions | | | | |
| Bypass surgery | 188 (45.0%) | 33 (55.0%) | 155 (43.3%) | |
| Endovascular treatment | 230 (55.0%) | 27 (45.0%) | 203 (56.7%) | 0.095 |

HTN: hypertension; DM: diabetes mellitus; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TG: triglyceride

events (restenosis >75% in diameter or occlusion) occurred in 60 lesions, including iliac for 19 and infrainguinal lesions for 41 (femoral artery for 37 and popliteal artery or below for 4 lesions), in 51 patients (VE group). Of 60 lesions with local vascular events, 25 lesions (41.7%) were developed among the TASC II type A or type B lesions, and 35 lesions (58.3%) were among the TASC II type C or type D lesions. Local vascular events significantly occurred more frequently in TASC II type C or D lesions than in type A or B lesions (*P* = 0.025). Regarding the difference in treatments for vascular lesions, 33 lesions (55%) occurred in patients undergoing surgical procedures and 27 lesions (45%) in those undergoing EVT (*P* = 0.095; not significant, NS). In univariate analysis of clinical characteristics between the VE and NoVE group, there were no significant differences in age and gender, the prevalence of treatment for HTN or DM, statin drugs prescription, and the prevalence of hemodialysis. Treatment for CAD, including percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG), was required for 30 patients (PCI for 27 and CABG for 3 patients) before or after treatment of PAD. The prevalence of treatment for CAD in the VE group was not significantly different from the prevalence in the NoVE group ($P = 0.193$). Patients in the VE group showed a significantly higher post-therapeutic LDL-C level (120.4 ± 31.2 vs. 108.2 ± 25.1 (mg/dL); $P = 0.01$) than those in the NoVE group and a higher prevalence of infrainguinal lesions relative to iliac lesions ($P < 0.001$). Regarding the comparison between the pre- and post-therapeutic serum lipid levels, the post-therapeutic HDL-C levels (post-therapeutic 49.1 ± 13.9 vs. pre-therapeutic 43.6 ± 13.0 (mg/dL)), LDL-C levels (post-therapeutic 109.9 ± 26.2 vs. pre-therapeutic 116.1 ± 30.7 (mg/dL)) and the LDL-C/HDL-C ratio (post-therapeutic 2.45 ± 0.89 vs. pre-therapeutic 2.90 ± 1.17) were all significantly improved compared to the pre-therapeutic values ($P < 0.001$). The post-therapeutic TG levels (140.3 ± 62.5 mg/dL) were not different from the pre-therapeutic levels (139.3 ± 72.7 mg/dL) ($P = 0.771$).

The mean follow-up period until the endpoint of this study was 55.5 ± 38.9 (range 4 to 120) months for the NoVE group, which was significantly higher than those for the VE group (32.9 ± 28.8 (range 4 to 113) months) ($P < 0.001$). The difference in the follow-up period between the two groups may result from the presence or absence of local vascular events occurrence, which was the endpoint of this study. There were 32 deaths (10.4%) during the follow-up period, including deaths from malignancy (n = 5), pneumonia (n = 4), myocardial infarction and/or heart failure (n = 4), sepsis and/or multiple organ failure (n = 2), perforation or necrosis of the digestive tract (n = 2), mediastinitis (n = 1), and unknown cause (n = 14). These cases were represented as censored cases in the calculation of the Kaplan-Meier method.

As the TASC II type C/D has been reported as a predictor for adverse outcome after treatment of PAD,[6,11] we examined in more detail the relationship between local vascular events occurrence and the site and type of lesions classified with TASC II guidelines. **Table 2** summarizes the number of lesions classified with TASC II according to the type of treatment and the site of the lesion, and the relationship with development of later local vascular events. As shown in **Table 2**, local vascular events occurred more frequently in TASC II type C/D lesions compared to type A/B lesions in the total patients group (odds ratio 1.90; 95%CI 1.09–3.30; $P = 0.025$). For comparison of vascular events rate in patients undergoing bypass surgery and EVT individually, difference did not reach statistical significance, probably due to the small number of patients in each group. The prevalence of TASC II type C/D lesions was significantly higher in infrainguinal lesions ($P < 0.001$) and in patients undergoing surgery than in those undergoing EVT ($P < 0.001$).

Subsequently, clinical factors that may be related to the development of local vascular events were assessed with multivariate analysis using Cox proportional hazard model with stepwise method to identify correlations with the later events occurrence. The items assessed included male gender (vs. female), surgical treatment (vs. EVT), the presence of DM, CAD requiring PCI or CABG, infrainguinal lesions (vs. iliac lesions), TASC II type C/D lesions (vs. type A/B lesions) pre-therapeutic TG levels <140 (mg/dL), and post-therapeutic LDL-C levels <130 (mg/dL), which were selected based on the p value in the univariate analysis. The cut-off values of LDL-C and TG levels were calculated from receiver-operating characteristics curves (ROC curves) using statistical software. The results are shown in **Table 3**, which indicated that the infrainguinal lesions relative to iliac lesions significantly increased in the risk for later, local vascular events (hazard ratio 3.38; 95%CI 1.60–7.10; $P = 0.001$) and the lowered LDL-C levels <130 (mg/dL) decreased in the risk for later vascular events (hazard ratio 0.34; 95%CI 0.17–0.67; $P = 0.002$). In contrast, gender male ($P = 0.550$), surgical treatment relative to EVT ($P = 0.731$), presence of DM ($P = 0.865$), CAD requiring PCI or CABG ($P = 0.129$), TASC II type C/D (vs. type A/B) ($P = 0.937$), and pre-therapeutic TG levels <140 (mg/dL) ($P = 0.966$) did not significantly influence the risk for later vascular events.

Based on the results from multivariate analysis, we compared the rate of freedom from later local vascular events (VE-free rate) between the two groups divided according to the post-therapeutic LDL-C level. **Figure 1** shows a comparison of Kaplan-Meier curves indicating the VE-free rate, with a significant difference between the two patient groups. Patients with post-therapeutic LDL-C levels <130 mg/dL had a significantly better VE-free rate ($P = 0.005$; by the logrank test). A cumulative rate free from vascular events was approximately more than 90% for the 5 year and more than 80% for the 10 year in those with post-therapeutic LDL-C levels <130 mg/dL. The rate was, however, lower in those with post-therapeutic LDL-C levels >130 mg/dL, which was less than 80% for the 5 year and 10 year. Onset of vascular events, which was defined as the endpoint of the study in the VE group, was 32.9 ± 28.8 (months) as described previously and shown in **Table 1**.

**Table 2 The number of lesions classified with TASC II according to the type of treatment and site of lesion, and the relationship with development of later vascular events**

| | | The number of lesion classified with TASC II | | *P* value | Odds ratio (95% CI) |
|---|---|---|---|---|---|
| | | Type A or B | Type C or D | | |
| Iliac lesion | | 168 | 60 | | |
| Infrainguinal lesion | | 63 | 127 | <0.001 | 5.64 (3.70–8.61) |
| Local vascular events (total) | | | | | |
| | Yes | 25 | 35 | | |
| | No | 206 | 152 | 0.025 | 1.90 (1.09–3.30) |
| Local vascular events in patients undergoing bypass surgery | | | | | |
| Iliac lesion | Yes | 0 | 4 | | |
| | No | 6 | 55 | | |
| Infrainguinal lesion | Yes | 0 | 29 | | |
| | No | 5 | 89 | | |
| total | Yes | 0 | 33 | | |
| | No | 11 | 144 | 0.217 | N/A (due to data containing zero) |
| Local vascular events in patients undergoing EVT | | | | | |
| Iliac lesion | Yes | 15 | 0 | | |
| | No | 147 | 1 | | |
| Infrainguinal lesion | Yes | 10 | 2 | | |
| | No | 48 | 7 | | |
| total | Yes | 25 | 2 | | |
| | No | 195 | 8 | 0.332 | 1.95 (0.39–9.70) |
| Comparison of the number of patients between bypass surgery and EVT according to the TASC II classification | | | | | |
| bypass surgery | | 11 | 177 | | |
| EVT | | 220 | 10 | <0.001 | 354.0 (147–852) |

EVT: endovascular treatment; N/A: not available

**Table 3 Relationship between risk factors and later vascular events by Cox proportional hazard analysis**

| | Hazard Ratio | 95% CI | *P* value |
|---|---|---|---|
| Clinical factors | | | |
| Gender, male (vs. female) | 0.77 | 0.33–1.81 | 0.554 |
| Surgical treatment (vs. EVT) | 1.42 | 0.72–2.80 | 0.317 |
| Diabetes mellitus | 1.06 | 0.55–2.04 | 0.867 |
| CAD requiring PCI or CABG | 0.21 | 0.03–1.56 | 0.128 |
| Infrainguinal (vs. iliac) lesion | 3.35 | 1.63–6.90 | 0.001 |
| TASC II type C/D (vs. type A/B) | 0.93 | 0.17–5.01 | 0.937 |
| Pre-therapeutic TG <140 | 0.99 | 0.51–1.92 | 0.969 |
| Post-therapeutic LDL-C <130 | 0.34 | 0.17–0.67 | 0.002 |

CI: confidence interval; EVT: endovascular treatment; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; LDL-C: low-density lipoprotein cholesterol; TG: triglyceride

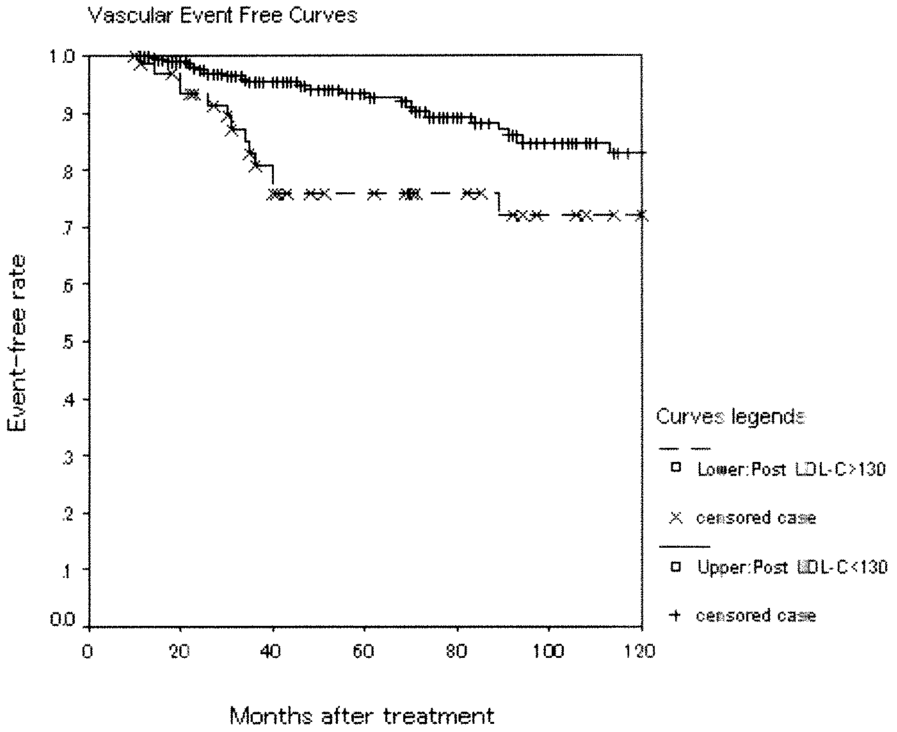

**Fig. 1** Kaplan-Meier curves indicating freedom from local vascular events in the group of patients with post-therapeutic LDL-C <130 and those with LDL-C >130 (mg/dL)

## DISCUSSION

Our data indicated that later, local vascular events after surgical or endovascular treatment for PAD may occur more frequently in patients treated for infrainguinal lesions and those with post-therapeutic mean LDL-C levels >130 (mg/dL), at an approximate hazard ratio of 3.0 to 3.5. PAD is a part of clinical manifestation of systemic atherosclerosis, and the presence of PAD elevates the risk for cardiovascular events due to atherosclerosis, including myocardial infarction and stroke.[2,3,5] Thus, of course, the prognosis of patients with PAD depends on the prevention of these systemic cardiovascular events, rather than on the presence or absence of local vascular events. However, local vascular events, such as restenosis and occlusion, may elevate the risk for development of CLI and amputation, and the reported annual mortality rate is as high as 25% in patients with CLI and in those undergoing major amputation.[6,14] Therefore, therapeutic strategy for preventing local vascular events may also contribute to the improvement of life prognosis in patients with PAD.

There have been a number of reports describing the value of using statin drugs in patients with PAD, including all cause and cardiac mortality.[3,15,16] LDL lowering therapy has been reported to improve symptoms of intermittent claudication and pain-free walking performance, and has also been reported to reduce the risk of new or worsening claudication in patients with PAD.[6,17] In the Heart Protection Study of cholesterol lowering with simvastatin, there was a 16% relative reduction in the rate of a first peripheral vascular event, primarily due to a 20% relative reduction in noncoronary revascularization procedures.[13] This study suggests that it may be the pleiotropic effects of statins that are responsible for benefit in PAD, including not only lipid-lowering effects but also anti-inflammatory effects. Statins have been also reported to reduce the expression of matrix metalloproteinases independently of their cholesterol-lowering effect.[6] However, the potential benefits of LDL lowering with statins on the underlying physiology in PAD remain incompletely understood.

The lipid level per se on individual cases may vary with pre-therapeutic lipid levels, racial variation, and individual lifestyle and comorbidity. There have been few reports describing the direct relationship between the serum lipid levels and later vascular events, especially in patients undergoing surgical treatment.[6] This is probably due to that those with PAD generally have a low chance of long-term survival,[5,6] which would inhibit the practice of this type of study. Furthermore, therapeutic strategy for patients with PAD has been changed in response to progress in EVT and publication of TASC and TASC II guidelines.[9,10] The majority of TASC II type A and type B lesions in iliac arteries are currently treated with EVT, and the number of patients undergoing open surgical procedures has been diminished. Thus, results from the present study including surgical cases are thought to be of significance. The cut-off value of LDL-C levels <130 mg/dL in this study was not a strict target value, as recent literature including AHA/ACC guidelines described that LDL-C should be <100 mg/dL for all patients with CAD and other clinical forms of atherosclerotic disease, and even <70 mg/dL in patients at the highest risk.[18,19] The optimal target LDL-C levels in Japanese patients with atherosclerotic disease may be different,[20,21] but later local vascular events occurrence showed a significant difference between patients with LDL-C levels <130 and those with LDL-C levels >130 mg/dL in this study. The target value of LDL-C levels <130 mg/dL seems to be the minimum requirement in the treatment of Japanese patients with PAD to reduce local vascular events.

Regarding the comparison between the pre- and post-therapeutic serum lipid levels, the post-therapeutic HDL-C, LDL-C, and LDL-C/HDL-C ratio were all significantly improved compared to pre-therapeutic values. This was probably due to the management of atherosclerotic risk factors including statin treatment, although aggressive lipid-modifying medications were not always performed during the follow-up period. Lifestyle guidance like diet and exercise therapy has been intensively conducted by medical personnel in the outpatient clinic throughout the follow-up period, which may have contributed to the improvement of lipid levels.

Our study also indicates that patients with infrainguinal lesions are at high risk for later local vascular events occurrence. As shown in **Table 2**, TASC II type C/D lesions comprised 127 of 180 (70.6%) infrainguinal lesions, whereas, 60 of 228 (26.3%) iliac lesions. The prevalence of the type C/D lesion, which has been reported to significantly influence graft patency in surgical cases, was further higher in infrainguinal lesions (*P* <0.001). The difference in the prevalence of the type C/D lesion may account for the high risk for later local vascular events occurrence in patients with infrainguinal lesions, but the Cox proportional hazard analysis did not indicate the TASC type C/D as a significant predictor for total later vascular events in our study. The disparity between the results from univariate analysis and the Cox proportional hazard analysis may be due to the onset time of vascular events, as the latter analysis investigated the effects of predictor over the time course.

The subjects in this study were limited to those under the age of 70 to ensure sufficient follow-up period and to minimize the influence of aging on local vascular events. In younger patients presenting with IC, however, the value of surgical revascularization remains to be elucidated.[22,23] Reed and colleagues reported that the 5 year primary patency rate after aortobifemoral bypass was significantly lower in patients aged 50 or younger than in those over the age of 50.[23] In the report by Green and colleagues, patency rates of primary prosthetic above-knee femoropopliteal bypass grafts at 5 years were lower in patients aged 65 or younger.[22] The underlying pathogenesis in these younger patients would be the presence of multiple atherosclerotic risk factors including dyslipidemia, which may account for the development of PAD in younger patients. Risk reductions in atherosclerotic factors among younger patients would be an important issue for the improvement of prognosis of overall patients with PAD.

The present study did not examine later cardiovascular events such as myocardial infarction and stroke, but limited to local vascular events after treatment of PAD. Lipid-modifying therapy in those with PAD, however, would be highly beneficial in the prevention of later cerebrovascular or coronary events. For the primary prevention of atherosclerotic disease like CAD, the importance of adequate control of dyslipidemia has been reported, and lipid-modifying therapies like statin treatment have an established role in the treatment of occlusive atherosclerotic disease.[18,24] In general, LDL-C at a high serum level may accumulate in the artery wall, where they are oxidized and taken up by foam cells, in a process that leads to the development and progression of atherosclerosis.[24] HDL-C is reported to oppose atherosclerosis by removing cholesterol from foam cells, by inhibiting the oxidation of LDL-C, and by limiting the inflammatory processes that underlie atherosclerosis.[24] As previously described, the definite prognosis of patients with PAD depends on the prevention of fatal CAD and cerebrovascular disease. In patients with AAA, our group has reported the relationship between the lipid levels and later cardiovascular events after surgical treatment for AAA.[25] The relationship between lipid levels and later cardiovascular events in patients with PAD would be also worth reporting.

There are some limitations in this study. In our study design, patients with PAD receiving surgical or endovascular treatment were retrospectively divided into two groups, based on the patient outcome of whether they would have local vascular events later or not, as a single center experience. Lipid-modifying therapy was not given to all patients. Second, the findings of our study were limited to those aged <70 at surgical or endovascular treatment; thus the value of lipid-modifying therapy in patients with age older than the present study group is unknown. Since the majority of subjects were male patients, we can draw no conclusions on the association of lipids with local vascular events in women. Third, the follow-up period was relatively short in some patients; thus, the short follow-up period may influence the incidence of local vascular events. Although there are many limitations, our study results are not so inconsistent with previous reports and may help us to prognosticate the outcome at least in part of patients with PAD.

In conclusion, our study indicated that an increase in the post-therapeutic LDL-C levels >130 mg/dL and the presence of infrainguinal lesions were significant predictors for the development of later local vascular events during follow-up after surgical or endovascular treatment for PAD. Patients at high risk for later, local vascular events should require a careful follow-up to prevent the development of CLI or amputation, and may also require an aggressive lipid-modifying therapy.

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**Case Report**

# Adventitial Cystic Disease of the Popliteal Artery

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**We describe a patient with adventitial cystic disease of the popliteal artery with intermittent claudication involving the right calf during exercise. Magnetic resonance imaging (MRI) and computed tomography (CT) revealed a cystic lesion that encircled and compressed the popliteal artery. Resection of the cyst involving a segment of the affected popliteal artery and interposing an autologous vein graft resolved the symptoms, and the postoperative course was uneventful. The cyst was histologically similar to a ganglion.**

***Keywords:*** intermittent claudication, autologous vein graft, ganglion

## INTRODUCTION

Adventitial cystic disease is a rare vascular condition that mainly affects the popliteal artery[1)] and usually presents as intermittent claudication during exercise. We describe the recent management of an otherwise healthy adult man who developed intermittent claudication of the calf while walking.

## CASE REPORT

A 45 year-old man was referred to an orthopedic clinic with right calf pain after walking for 10 minutes. Three months of drug therapy did not relieve this symptom, and he was referred to our clinic for evaluation of a vascular disorder. A physical examination revealed palpable right popliteal and foot pulses at rest that persisted during knee flexion. The right and left ankle-brachial pressure indices were 1.32 and 1.22, respectively. Other clinical and laboratory findings were normal, and he was in good health except for mild hypertension and mild hyperlipidemia.

Magnetic resonance imaging (MRI) proceeded in the axial and sagittal planes. T2-weighted imaging revealed a multi-loculated cystic mass with high signal intensity measuring 25 × 30 × 45 mm in the popliteal fossa of the right knee. A cystic mass was adjacent to and encircled the popliteal artery (**Fig. 1A**). The cyst had a thin wall and no solid contents (**Fig. 1B**). The signal characteristics of the mass were comparable with those of ganglion on T2-weighted images, and the intensity was homogeneously low on T1-weighted images.[2,3)]

Contrast-enhanced computed tomography (CT) showed that the popliteal artery was compressed by a non-enhancing structure related to the arterial wall. The typical hourglass sign (concentric, extrinsic compression) of the popliteal artery seen on three-dimensional CT angiograms is shown in **Fig. 2**.[3)]

Adventitial cystic disease of popliteal artery was diagnosed and surgery was scheduled. An S-shaped skin incision was cut linear to the skin fold in the right popliteal fossa under general anesthesia with the patient in the prone position throughout the procedure. After dissection, a round, loculated cystic lesion encircling the popliteal artery was identified (**Fig. 3**). The cyst was soft, elastic and contained a clear jelly-like substance. The dense adhesion ruled out cyst evacuation to preserve the popliteal artery and incomplete resection might have led to recurrence. We completely resected the cyst and the affected segment of the popliteal artery and reconstructed the artery using a great saphenous vein graft.[1,4)] Histopathologically, the cyst had a relatively clear margin with vascular adventitia. The cyst had no arterial elements

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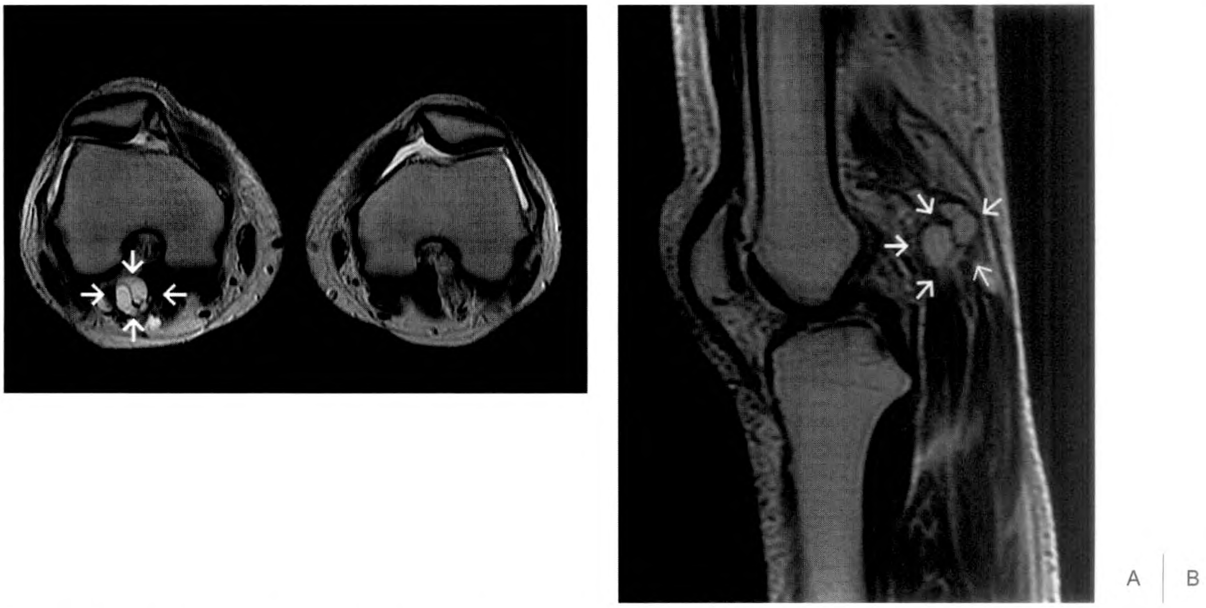

**Fig. 1** T2-weighted magnetic resonance images.
**A**: Multi-loculated, high-intensity cystic mass (white arrow) measuring 25 × 30 × 45 mm is located in right popliteal fossa. **B**: Sagittal view shows popliteal artery surrounded and compressed by cystic mass (white arrow).

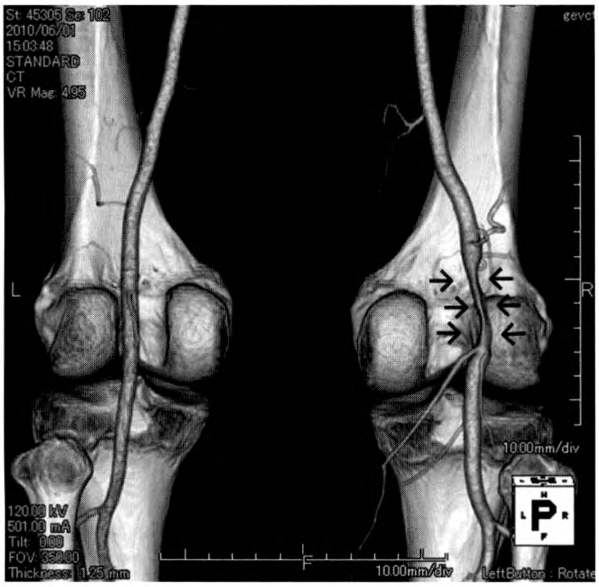

**Fig. 2** Three-dimensional CT angiographic image.
Typical hourglass sign of popliteal artery (black arrow); arterial lumen is encircled by cyst and concentrically compressed. No atherosclerosis is evident in the remaining part of the artery.

in the wall and mucinous content, which were consistent with a ganglion. The postoperative course was uneventful, and the patient was free of right calf claudication. The condition did not recur, and three-dimensional CT angiography, six months later, showed good patency of the vein graft.

## Discussion

Adventitial cystic disease is rare, accounting only for 0.1% of all vascular diseases.[1] Atkins and Key first described adventitial cystic disease in 1947 that affected the right external iliac artery.[5] Over 300 cases have been reported since then. Adventitial cystic disease affects the popliteal artery unilaterally (85%) most often and usually presents as intermittent claudication, although bilateral involvement[6] has also been reported and the external iliac, common femoral, radial and ulnar arteries have been affected.[4,6]

Over 80% of individuals who develop adventitial cystic disease are men aged between 40 and 50 (range of 11–70) years, and the prevalence of this disease is 1:1200 cases of calf claudication.[1] Because the affected population is usually young and at low risk for vascular disease, a clinical diagnosis is often difficult. Adventitial cysts compress the arterial lumen in an eccentric or concentric fashion and appear as scimitar or hourglass signs, respectively, on angiograms.[2,3] The severity of ischemic symptoms varies, and mainly depend on the condition of the affected popliteal artery. However, even if the affected popliteal artery appears angiographically normal, adventitial cystic

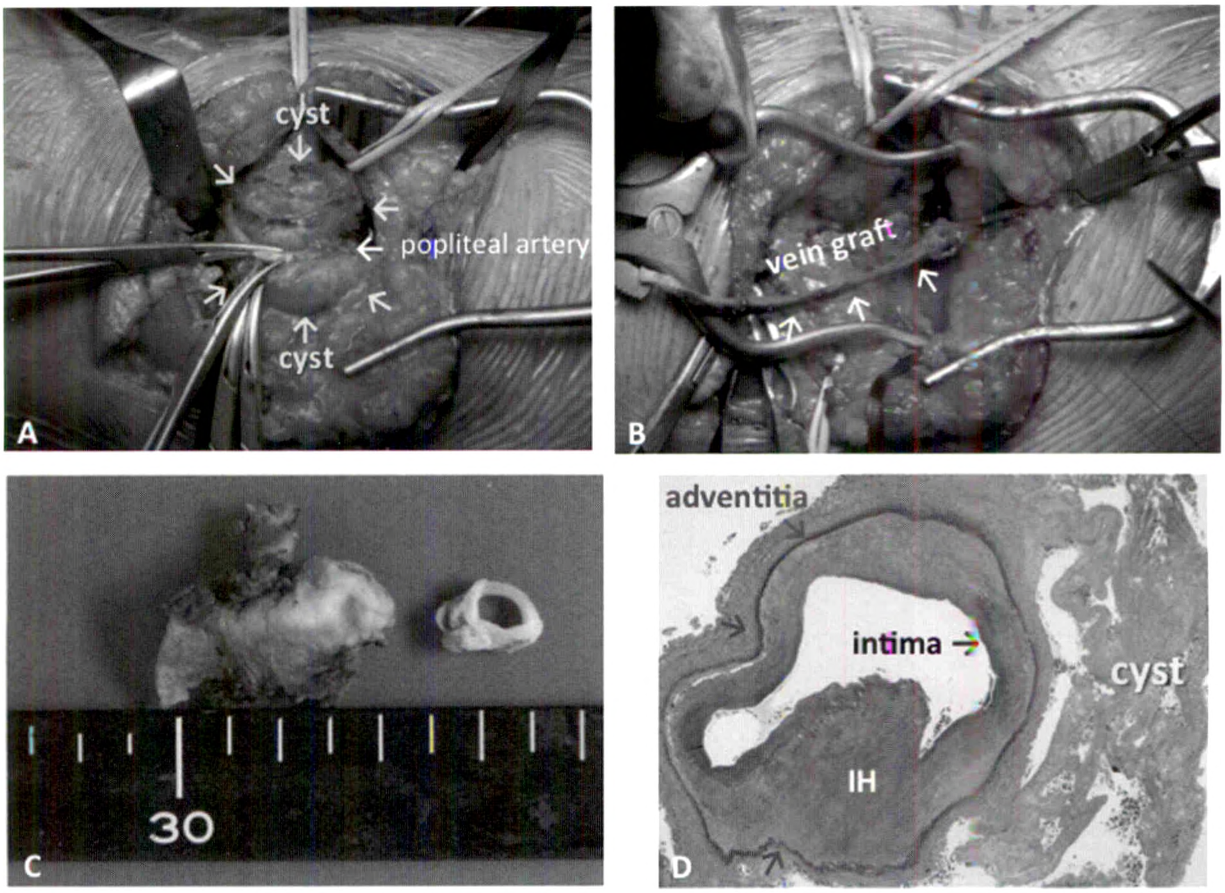

**Fig. 3** Intra-operative findings and surgical specimen.
**A**: Popliteal artery surrounded by loculated cyst is concentrically compressed and severely narrowed. **B**: Segment of popliteal artery surrounded by cyst has been resected, and reconstructed using interposing vein graft. **C**: Surgical specimen comprising resected segment of popliteal artery with adjacent cyst. **D**: Microscopy shows popliteal artery surrounded by cyst with cavity and defect in the adventitia of popliteal artery. Cyst wall has no vascular elements and forms a clear margin with popliteal artery. Arterial lumen is narrowed by intimal hyperplasia (IH). (Elastica Masson stain × 20)

disease can induce symptoms during exercise. Adventitial cystic disease is considered to cause functional flow obstruction during dynamic exercise.[6] Because the pulse in the right foot of our patient was normal at rest but diminished after exercise when symptoms developed, surgery was required to relieve the symptoms.

The etiology of adventitial cystic disease is still under debate, and trauma, ganglion, systemic disorder, and embryonic development have been proposed. The trauma theory suggests that repetitive trauma causing degeneration of the arterial adventitia ultimately leads to cystic change. The ganglion theory suggests that synovial cysts form nearby joints track along vascular branches and finally reside in the adventitia of major vessels. The systemic disorder theory perceives adventitial cystic disease as a part of generalized connective tissue disorder. The developmental theory suggests that mesenchymal cells rich in mucin from nearby joints incorrectly migrate to the adventitia during embryogenesis. However, no single theory can account for the pathogenesis of all clinical cases. Levien et al. proposed a unifying hypothesis on the basis of embryology of susceptible blood vessels and the affected site. They claim that a joint-related ganglion-like structure is incorporated into a target vessel during embryological development and that this synovial rest or ganglion secretes and enlarges over the years to develop within the adventitial wall later in life, implying that both the ganglion and developmental theories are applicable.[7,8]

The typical, pathological findings of adventitial cystic disease comprise intramural cysts containing gelatinous material located between the media and the adventitia. The cyst was in contact with the popliteal artery but located outside the adventitia in our patient. The cyst had mucinous content but no vascular elements in the wall. These findings were similar to those on ganglion and are inconsistent with most reported cases. However, Ohta et al. described recurrent adventitial cystic disease in an interposed vein graft and found a compressed lumen with intimal hyperplasia and no evidence of intra-adventitial invasion of the vein graft. They postulated that mucin-secreting synovial cells originating from neighboring joint capsule had directly invaded damaged adventitia or had simply attached to and encircled the adventitia.4) The pathological findings of our surgical specimen support this hypothesis.

Gray scale Doppler ultrasonography (U.S.) is a less invasive, convenient diagnostic method for routine clinic application, whereas CT and MRI are more useful for evaluating cyst morphology and possible communication between a cyst and an adjacent joint. The MRI findings of adventitial cystic disease are quite clear as cysts typically appear as regions of homogeneous, low signal intensity on T1-weighted images, and of multi-loculated high signal intensity adjacent to vessels on T2-weighted images. Three-dimensional CT reconstructions using volume rendering or MRA should be performed for optimal preoperative planning. Conventional digital subtraction angiography (DSA) is rarely applied because this modality is invasive.2,3) The differential diagnosis includes popliteal artery entrapment syndrome (PAES), and multi-planar data acquisition can determine the anatomical extent of arterial intramural cystic lesions, thus helping to discriminate this condition from adventitial cystic disease.9)

The management of adventitial cystic disease varies depending on the condition of the affected vessels. Cyst aspiration is less invasive, but it is associated with a high rate of recurrence. Removal of the cyst content (evacuation) while preserving the involved artery can be effective and resection of the affected segment of the vessel and interposing a vein graft or prosthesis is promising. Long-term follow-up is mandatory because adventitial cystic disease can recur or grafts can become occluded. Endovascular interventional therapy has yielded unsatisfactory outcomes.4,10)

Adventitial cystic disease of the popliteal artery is an uncommon but important cause of peripheral vascular insufficiency in younger individuals without specific atherosclerotic risk factors. Thus, adventitial cystic disease should be considered when relatively young individuals present with intermittent claudication.10)

## CONCLUSIONS

We described a patient with adventitial cystic disease of the popliteal artery with intermittent claudication. The cyst involving the affected popliteal artery was resected, and an autologous vein graft was interposed. The patient remained free of symptoms after the procedure, and postoperative three-dimensional CT images showed good patency of the vein graft. Long-term follow up is mandatory because of the potential for recurrence or graft occlusion.

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**Case Report**

# Surgical Reconstruction for Intrathoracic Aneurysm Originating from Proximal Part of the Right Subclavian Artery

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Keikou Tei, MD and Yuuki Horio, MD

**Subclavian artery aneurysms are comparatively rare in peripheral aneurysms. We experienced a case of intrathoracic aneurysm originating from the proximal part of the right subclavian artery. A 78 year-old man was referred to our hospital with the diagnosis of a right subclavian artery aneurysm. Enhanced computed tomography demonstrated an intrathoracic aneurysm, originating from the right subclavian artery just proximal of its origin. Through a median sternotomy and supra-infraclavicular incision, we reconstructed the brachiocephalic and right common carotid arteries and bypassed to the distal part of the right subclavian artery by using a T-shaped vascular graft and the aneurysm was excluded.**

***Keywords:*** subclavian artery aneurysm, intrathoracic aneurysm, graft replacement

## INTRODUCTION

Subclavian artery aneurysm is a rare aneurysm; its incidence has been reported as 3.5% of all peripheral aneurysms.[1] The surgical procedure and approach depend on the size and location of the aneurysms.[2] We experienced a surgical case of intrathoracic aneurysm originating from the proximal part of the right subclavian artery. We discuss the relation between the location of an aneurysm and the surgical procedure.

## CASE REPORT

A 78 year-old man, who had gone to the hospital because of hoarseness, was pointed out to have a mediastinal mass by computed tomography (CT). At that time, positron-emission tomography denied the malignancy of the mass, and it had been observed. Eight years later, it developed a tendency to increase in size, and he was referred to our hospital for surgery. He had no history of trauma, and no pulsatile mass was found at his supraclavicular fossa on physical examination. A chest radiograph indicated an intrathoracic mass in the right upper thorax. Contrast-enhanced and three-dimensional reconstructed CT demonstrated an intrathoracic aneurysm, which was 60 × 58 mm in size, and it originated from the right subclavian artery just proximal of its origin (**Fig. 1A** and **1B**). Brain magnetic resonance angiography showed complete communication of the circle of Willis; however, the vertebral artery was left dominant (**Fig. 1C**). Therefore, we monitored the regional saturation of oxygen ($rSO_2$) of the brain with the INVOS 5100C cerebral oximeter (Somanetics, IL, USA) during operation.

We started an operation via median sternotomy and right supraclavicular incision. At first, through a median sternotomy, the brachiocephalic artery, right common carotid artery and right subclavian aneurysm were identified. However, the distal side of the aneurysm was not well approached through these incisions because of dense adhesion between the aneurysm and surrounding tissues. After systemic heparinization, clumping the brachiocephalic artery, the right cerebral clamping $rSO_2$

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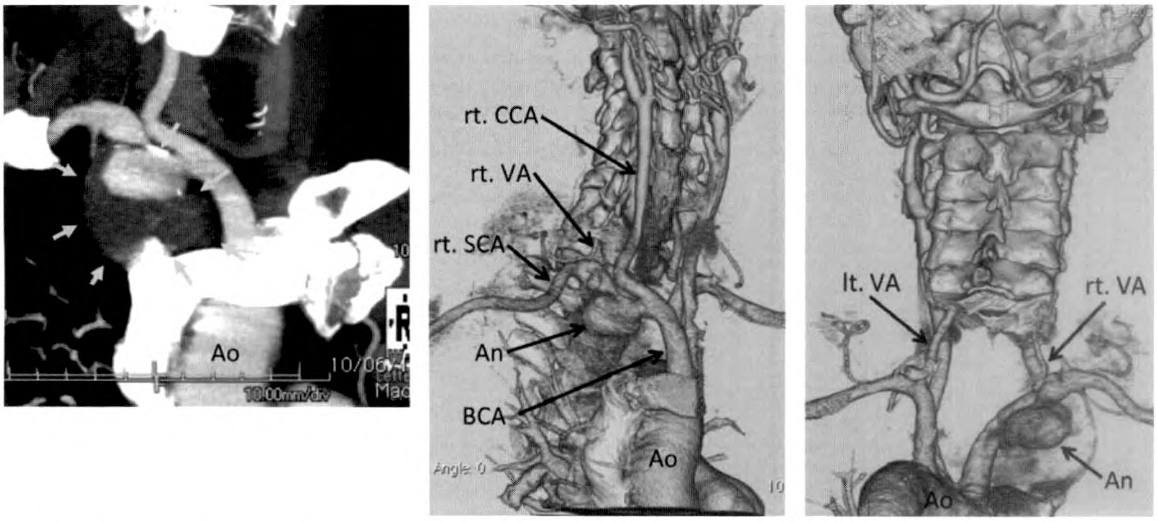

**Fig. 1** Preoperative computed tomography (CT) findings.
**A**: The right anterior oblique view of enhanced CT, the aneurysm was originated from the right subclavian artery just proximal of its origin (arrows).
**B**: The three-dimensional CT (3D-CT) from right anterior oblique view.
**C**: The 3D-CT from posterior view demonstrated that the vertebral artery was left dominant.
Ao: aorta; BCA: brachiocephalic artery; An: aneurysm; rt. SCA: right subclavian artery; rt. VA: right vertebral artery; lt. VA: left vertebral artery; rt. CCA: right common carotid artery

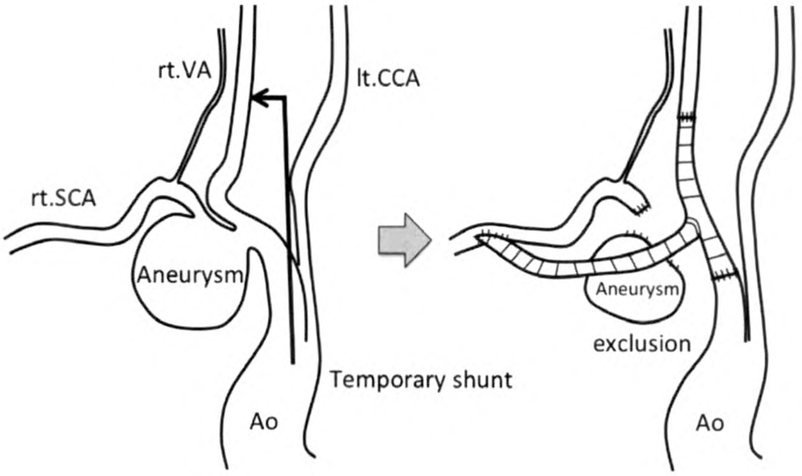

**Fig. 2** The schema of operation. We reconstructed the brachiocephalic and right common carotid arteries, and bypassed to the distal part of the right subclavian artery by using a T-shaped vascular graft, and the aneurysm was excluded.
Ao: aorta; rt. SCA: right subclavian artery; rt. VA: right vertebral artery; rt. CCA: right common carotid artery; lt. CCA: left common carotid artery

dropped; thus, we decided to use a temporary shunt. We inserted a shunt needle into the ascending aorta as an inflow source, and then the right common carotid artery was perfused from this shunt. After this shunting, the brachiocephalic artery was clamped again, and the right cerebral $rSO_2$ was maintained. During this temporary shunt, we reconstructed the brachiocephalic and right common carotid arteries by using a T-shaped knitted Dacron vascular graft through a median sternotomy. Concerning the reconstruction of the right subclavian artery, it was difficult to anastomose in an end-to-end fashion, just distal to the aneurysm; therefore, we added an infraclavicular incision and bypassed the graft to the distal part of the right subclavian artery through this incision. After the complete reconstruction using a T-shaped graft, the aneurysm was excluded, and the right subclavian artery was closed as a stump at just distal side of the aneurysm (**Fig. 2**).

Postoperatively, the patient achieved complete remission and was discharged from the hospital on day

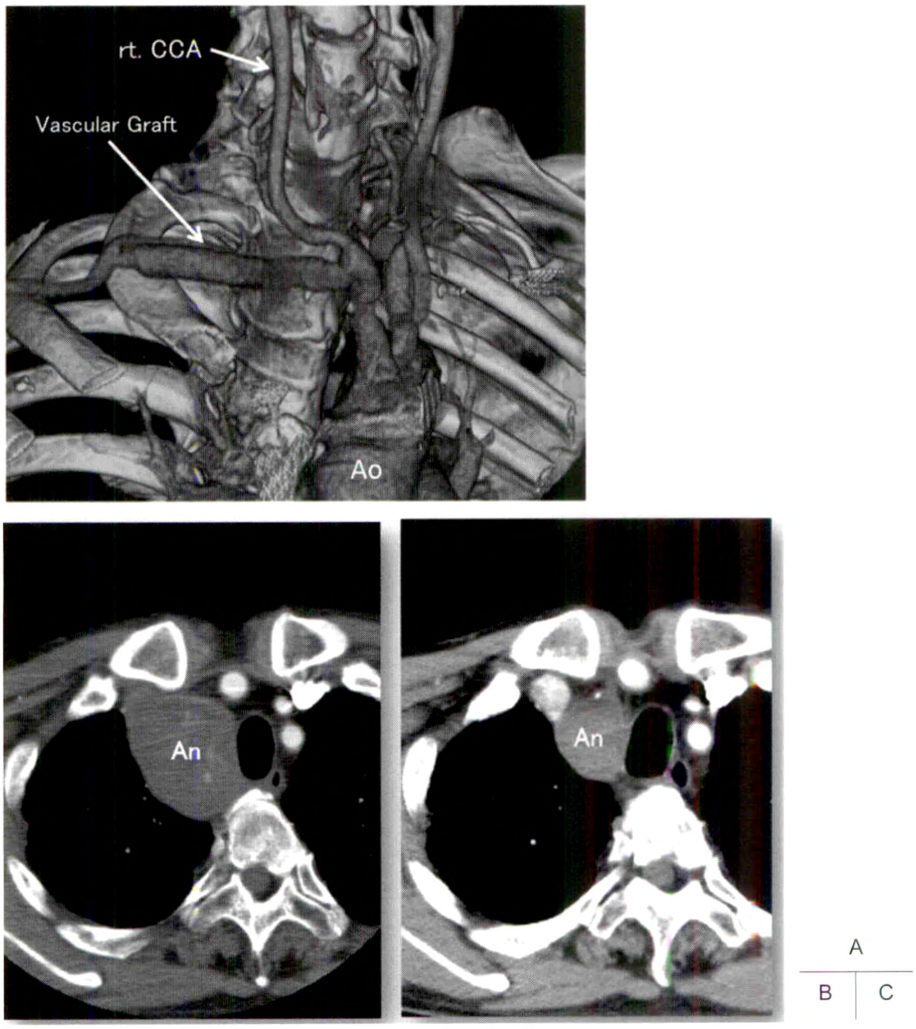

**Fig. 3** One year follow up computed tomography.
**A**: One year follow up three-dimensional computed tomography showed the graft patency.
**B**: The axial view of preoperative enhanced computed tomography.
**C**: The axial view of 1 year follow up enhanced computed tomography showed a regression of the excluded aneurysm (compared with **Fig. 3B**).
rt. CCA: right common carotid artery; Ao: aorta; An: aneurysm

21 after the operation. At 1 year of follow up, contrast-enhanced CT demonstrated graft patency and reduction in the size of the excluded aneurysm (**Fig. 3**).

## DISCUSSION

Subclavian artery aneurysms are rare, and there is the possibility of life- and limb-threatening complications, such as thrombosis, embolism, and rupture. The subclavian artery has intra-thoracic and extra-thoracic parts while anatomically, it may be divided into three parts.[3] The practical categorization into three parts has been suggested as follows: proximal, middle and distal parts.[4] The proximal part extends from the origin, with the brachiocephalic artery on the right side and aorta on the left, to the medial border of the scalene muscles. The middle part of the subclavian artery is located dorsal to the anterior scalene muscles. The distal part of the subclavian artery extends from the lateral border of the anterior scalene muscle to the lateral border of the first rib.[4,5] Accordingly, intrathoracic aneurysms are mainly found in the proximal part. The majority (39%) of subclavian artery aneurysms are located in the proximal segment of the subclavian artery, and the middle and distal segments account for 25% and 24%, respectively.[3] Furthermore, thromboembolic complications are mainly related to distal aneurysms, and middle and proximal aneurysms appear to have a tendency to rupture.

An operation should be considered in all cases because the risk of thromboembolic complications is unrelated to the diameter of the aneurysms.[3,6] The approach of surgery differs according to the location of the aneurysms. Aneurysms of the distal and middle part of the subclavian artery are easily exposed by a supraclavicular incision. If the surgical view is poor, and further exploration is required, an infraclavicular incision or clavicular division (or resection) may also be used.[3,7] Bito et al.[7] reported a successful case of exposing the middle part of the subclavian artery with a clavicular division, and concluded that dividing the clavicle is considered useful for achieving an adequate operative field to treat the vessel safely. Repair of these portions is usually achieved by resecting the aneurysm and vascular graft replacement.

The access and procedure for the proximal part of subclavian artery aneurysms is fairly complicated. It is essentially different from whether right or left because the right subclavian artery originates from the brachiocephalic artery and the left subclavian artery originates from the thoracic aortic arch. Proximal aneurysms of the left subclavian artery can be approached through a high, left posterolateral thoracotomy. Moreover, if aneurysms originate from only the ostium of the aorta, a median sternotomy (with left supraclavicular extension[8]) is necessary and aortic arch replacement may be able to be performed. On the other hand, access options for proximal right subclavian artery aneurysms are right thoracotomy or median sternotomy, if necessary, with supra or infraclavicular incisions. Several surgical techniques have been reported for proximal right subclavian artery aneurysms. Currently, it appears that arterial graft interposition or primary end-to-end anastomosis is common subsequent to aneurysmal resection.[2] We reconstructed the brachiocephalic and right common carotid arteries and bypassed to the distal part of the right subclavian artery because of the following reasons: First, the aneurysm extended from the origin of the subclavian artery (the innominate bifurcation); in this situation, it was difficult to reconstruct only the right subclavian artery because the proximal anastomotic neck could not be preserved. Second, the aneurysm was adhesive and large, so the distal anastomosis site of the subclavian artery could not be mobilized to anastomose in an end-to-end fashion from sternotomy and supraclavicular sides. Furthermore, separation of aneurysm was risky considering the bleeding. For these reasons, we decided to close as a stump at just distal side of the aneurysm with aneurismal exclusion and bypass to the distal part of the right subclavian artery. By excluding the aneurysm, there was concern about aneurysmal expansion due to the back pressure exerted by several inflow arteries toward the aneurysm. Salo et al.[9] recommend aneurysmal exclusion rather than resection; they suggest that exclusion is technically easier than resection and achieves the same postoperative long-term results. Although aneurysmal expansion due to back pressure is a possibility, in our case, enhanced CT at the 1 year follow-up showed that the excluded aneurysm had regressed. It is important to conduct further clinical follow-ups.

Concerning the reconstruction of the right carotid artery, preoperative assessment of craniocervical arteries by contrast enhanced CT and magnetic resonance imaging is necessary. In our case, the vertebral artery was demonstrated left dominant; therefore, we monitored the $rSO_2$ of the brain during operation. By monitoring with INVOS, we could decide whether to use a temporary shunt intraoperatively. Thus, an aorto-right common carotid temporal shunt should be established to ensure safety of the procedure and reduce the risk of cerebral ischemia and infarction. A preoperative knowledge of whether the brachiocephalic artery could be clumped, such as Matas test would be useful.

Conventional treatment for subclavian artery aneurysms is surgical repair and the use of endovascular repair has been increasing. Morbidity and mortality rates of open and endovascular repair are within the same range.[3] Vierhout et al.[3] described in a review of the literature that the subclavian artery is extremely mobile and exposed to rotational forces during abduction and ante-flexion of the arm. Therefore, a stent-graft has to be flexible and resistant to kinking and fracture. Furthermore, a variety of stent-grafts have been used to date. In-stent stenosis and thrombosis were observed in early series; however, in recent studies, the patency of stent-grafts appears to have increased. Patency results of endovascular treatment may further increase with the development of better stent-grafts and improved postprocedural pharmacotherapy. In our case, the endovascular repair seemed to be difficult. The subclavian artery aneurysm originated just innominate bifurcation. When we consider endovascular repair, the proximal landing zone could not be secured. Resch et al.[10] reported a combined open and endovascular approach for such an aneurysm of the innominate bifurcation. They achieved to deploy the endograft extending from the innominate into the common carotid artery with a carotid-subclavian bypass and ligation of the subclavian artery distal to the aneurysm. Their reported case was past history of ascending aortic repair combined with valve replacement. In such reoperative and high risk cases, an endovascular repair might be considered.

## CONCLUSION

We experienced an intrathoracic aneurysm of the proximal part of the right subclavian artery. We consider that entire brachiocephalic artery and right common carotid artery reconstructions are useful when the proximal anastomotic neck cannot be preserved. In cases where it is difficult to anastomose the distal side, it might be useful to close as a stump at just distal side of the aneurysm with aneurismal exclusion and bypass to the distal part of the right subclavian artery.

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**Case Report**

# Sural Artery Bypass in Buerger's Disease: Report of a Case

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**A 72 year-old man was admitted to the hospital to receive treatment for resting pain and an ulcer, which had developed on an amputation stump, 4 months after he had undergone a thrombectomy, below-the-knee popliteal-dorsal pedis artery bypass of his left leg, and digital amputation of his 2nd toe. Angiography demonstrated diffuse arterial and bypass occlusion in his left leg that did not include a sural artery, which was the main collateral. Therefore, the patient underwent reversed saphenous vein bypass from the common femoral artery to the medial sural artery. His leg pain disappeared, and the ulcer healed promptly.**

***Keywords:*** sural artery bypass, perigenicular artery bypass, collateral artery bypass

## INTRODUCTION

Revascularization is the primary option in the management of critical limb ischemia. Previous studies have described bypass to the perigeniculate collateral arteries as an option for limb salvage in selected patients, such as in cases of extensive disease, previous failed endo- or open vascular attempts, lack of the usual crural arterial runoffs or autogenous substitutes being common scenarios.[1–7] However, the use of this bypass has been restricted to a few groups of vascular surgeons. This report presents one case of a successful sural artery bypass in a patient with Buerger's disease, who presented with rest pain in the leg due to occlusion of the previous distal bypass.

## CASE REPORT

A 72 year-old man, who had smoked for fifty years, was diagnosed with diabetes mellitus. He had suffered the thrombophlebitis of his left leg one year earlier and was admitted to the hospital to receive treatment for coldness, cyanosis and severe rest pain in his leg and a painful ulcer, measuring approximately 8 mm in diameter, which had developed on the amputation stump of the left 2nd toe. He had undergone thrombectomy of his left leg 5 months earlier and left below-the-knee popliteal to dorsal pedis artery bypass using a reversed saphenous vein graft and amputation of the left 2nd toe 4 months earlier. His ankle-brachial pressure index was immeasurable. Electrocardiogram showed sinus rhythm and no ischemic changes. Computer tomography showed no embolic sources, no peripheral aneurysms nor evidence of popliteal entrapment. Angiography demonstrated diffuse arterial occlusion, occlusion of the superficial femoral artery, popliteal artery and crural artery of his leg and the bypass graft. However, the sural artery was dilated, and it was the main collateral to the calf (**Fig. 1**). He underwent arterial bypass from the common femoral artery to the medial sural artery with a reversed contralateral saphenous vein graft to treat the ischemic lower extremity. The medial sural artery was exposed via a medial approach. The skin incision was a classic medial below-the-knee

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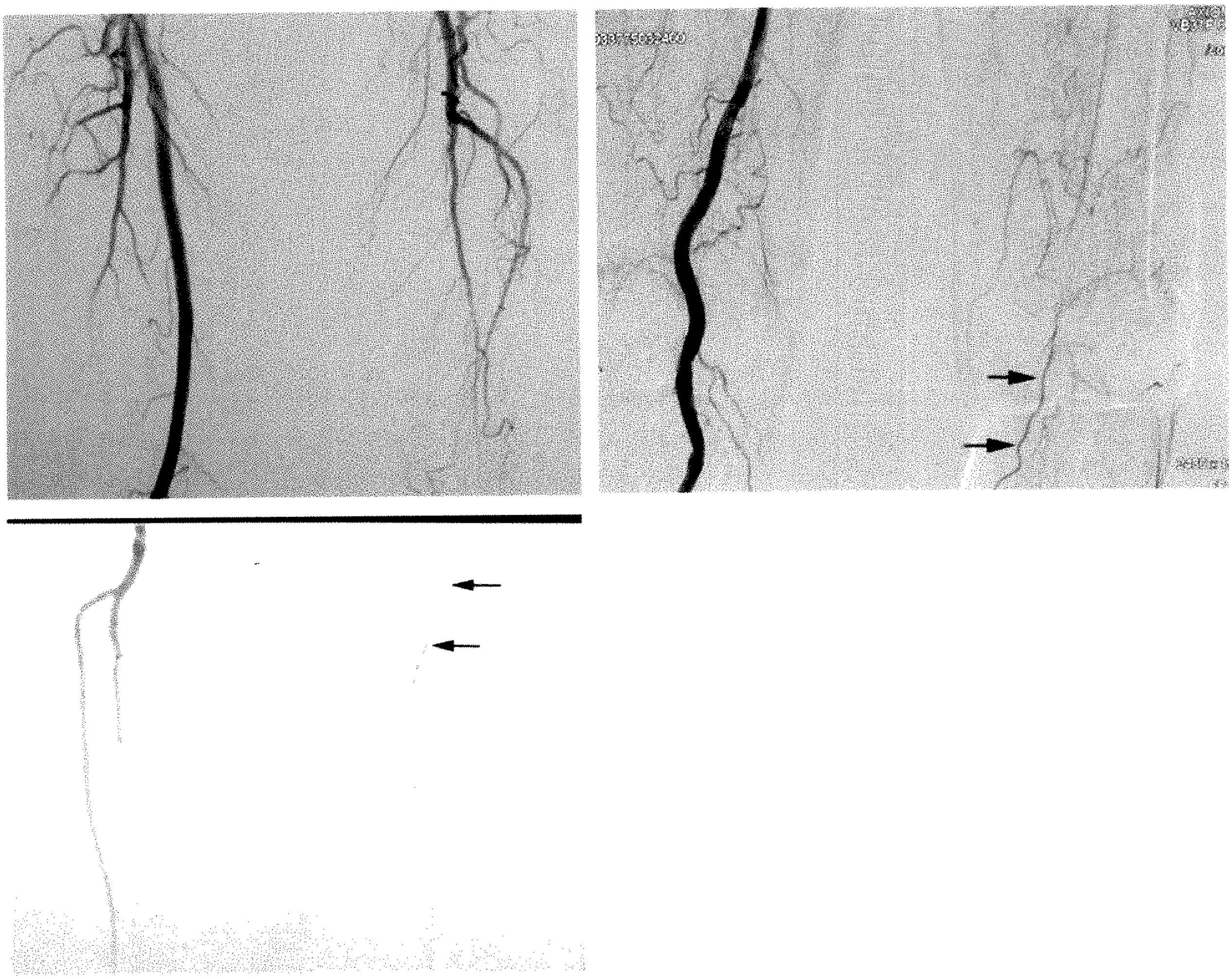

**Fig. 1** Pre-operative angiogram.
The left superficial femoral, popliteal and crural arteries were occluded. A dilated sural artery (arrow) was the main collateral to the lower leg.

popliteal incision extended to the proximal site along posterior edge of the semitendinosus muscle. The crural fascia was incised posteriorly toward the proximal site along the semimembranosus and semitendinosus muscle and peeled carefully from the surface of the medial head of the gastrocnemius muscle. The medial sural artery was exposed from its origin from the popliteal artery into the medial head of the gastrocnemius muscle surrounded by a venous plexus. There were two medial sural arteries and both of them were similar in size to the usual peroneal artery. One of them was going into the medial head of the gastrocnemius muscle deeply, so we decided the other one as a target vessel that seemed easier to anastomose in technically. The wall was not fragile, and there were no atherosclerotic changes. The distal anastomosis was performed with 6–0 polypropylene sutures using a pneumatic tourniquet to control bleeding, minimizing the extent of sural artery exposure and decreasing the risk of clamp injury (**Fig. 2**). Histopathological finding of the superficial femoral artery was supportive for Buerger's disease, as it showed mild inflammatory changes in tunia media and intimal thickening associated with fresh thrombosis.

The patient's postoperative course was uneventful. Though his postoperative ankle-brachial pressure index was still immeasurable, his foot became warm, and his leg pain disappeared. Postoperative angiography showed a patent bypass graft and good collateral blood flow to the calf muscle (**Fig. 3**). The patient was discharged 16 days following surgery. The ulcer shrunk promptly and healed two months after surgery.

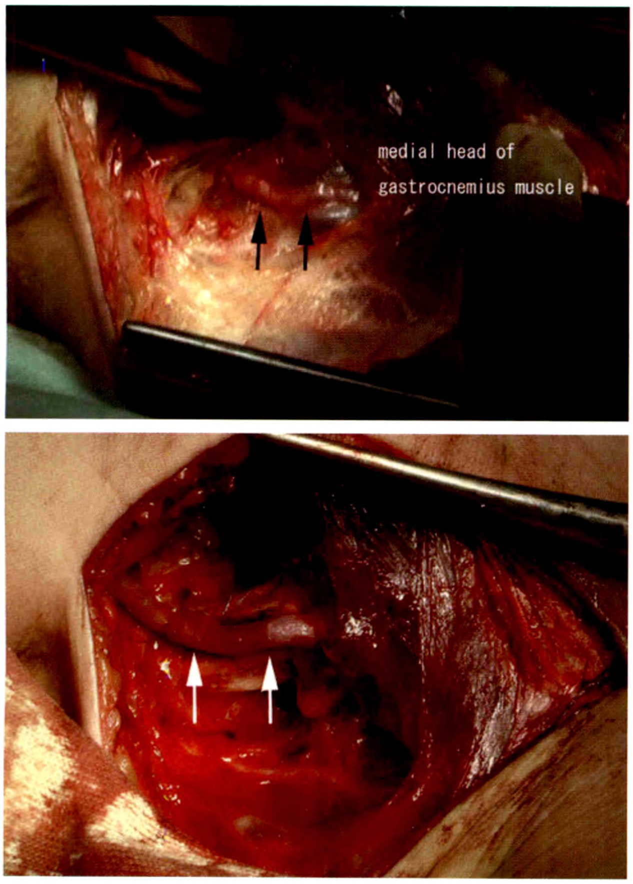

**Fig. 2** Intra-opetative findings.
**a**: The medial sural artery surrounded by a venous plexus (arrow) was exposed, arising from the popliteal artery and passing into the medial head of the gastrocnemius muscle.
**b**: A reversed saphenous vein graft (arrow) was anastomosed end-to-side to the medial sural artery using 6-0 polypropylene sutures.

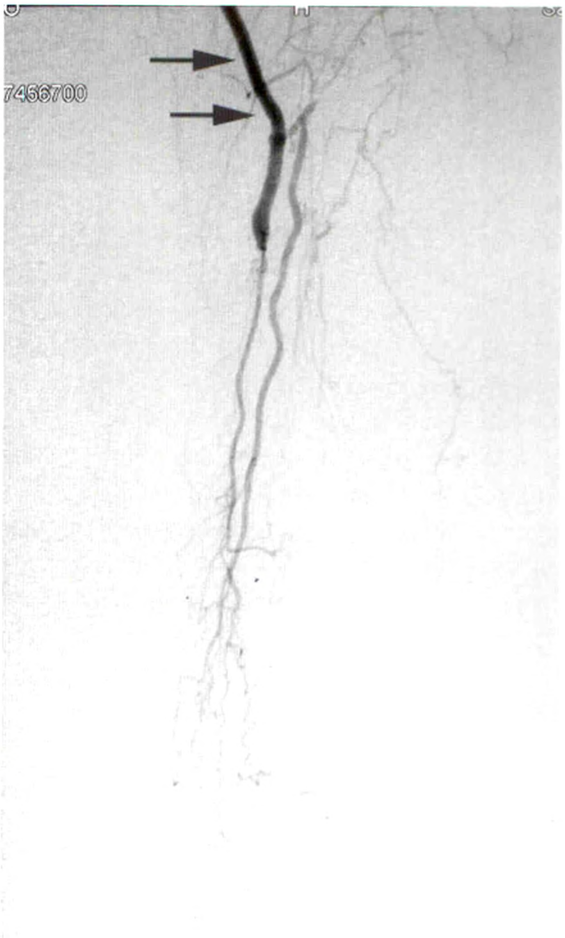

**Fig. 3** Post-operative angiogram.
The bypass graft (arrow) was patent, and good blood flow to the calf muscle was confirmed.

## DISCUSSION

Perigeniculate arteries are important collateral vessels in the lower leg, in patients with occlusion of the popliteal artery. Mannick et al. first reported that limb salvage could be achieved in patients with an isolated ("blind") popliteal artery segment (IPAS) by performing a femoropopliteal bypass with a reversed saphenous vein in 1967.[8] This procedure has been favored for patients with critical limb ischemia (CLI). Ballotta et al. reported that revascularizations to an IPAS can achieve acceptable results in terms of patency and limb salvage, with 3 year cumulative patency and limb salvage rates of 76% and 82%, respectively, even when there is no infrapopliteal runoff vessel.[9] Bypass to the perigeniculate collateral arteries is also described as an option for limb salvage in selected patients. Shindo et al. first reported a case of successful sural artery bypass for a patient with critical limb ischemia due to Buerger's disease in 1995.[1]

Two important collateral vessels are used for perigeniculate artery bypass, the highest genicular artery and the medial sural artery. The medial sural artery is one of the perigeniculate collateral vessels, and it arises from the posterior wall of the popliteal artery at the knee joint. de Latour et al.[3] reported that sural arteries present several advantages as distal anastomosis sites for lower limb bypass grafts. First, grafts to these arteries can be shorter, measuring between 25 and 35 centimeters, in length. Short conduit length not only improves graft quality but also increases circulatory velocity by reducing flow resistance. The second advantage is the availability of a good quality recipient artery. Like the internal thoracic artery, the perigeniculate collateral arteries are usually disease-free. This feature is especially important in patients with diabetes and renal insufficiency who often have calcified vessels. The third advantage of the perigeniculate collateral arteries is their mean diameter, i.e., 2–2.5 mm, comparable to that of the lower leg arteries. Brochado Neto et al. reported perigeniculate artery bypasses were performed to treat different combinations of advanced arterial disease, previously failed reconstructions, insufficient length of the available vein, and spreading infection in the affected limb.[4] De Latour et al.[3] and De Luccia et al.[6] reported that perigeniculate collateral artery bypasses can achieve acceptable results, in terms of patency and limb salvage rates, with 3 year primary, secondary patency, and limb salvage rates of 64.7%–74.7%, 69.9%–83.4% and 73.5%–90.2%, respectively.

Exposure of the sural artery through the medial approach seemed difficult because the mid portion of the popliteal artery is not usually used as a distal site of anastomosis in a femoro-popliteal artery bypass. Barral et al. described the surgical procedure for sural artery bypass.[2] They used a slightly lower incision in comparison to the classic medial above-the-knee popliteal incision for exposure of the sural artery. The sural arteries arise from the posterior aspect of the mid-popliteal artery, approximately 1 to 2 cm above the interarticular line. There is both a medial and a lateral sural artery, and they feed the respective heads of the gastrocnemius muscle, traveling with the sural branches of the tibial nerve. Barral et al. used the medial artery, which is surrounded by a venous plexus that is carefully freed down to the level at which the artery descends into the gastrocnemius muscle.[2] This muscle can be mobilized and divided for 1 to 2 cm to allow the exposure of an additional 3 to 4 cm of artery. One of the advantages of this procedure is that this allows the surgeon to completely avoid below-the-knee incisions, which are more likely to present wound-healing difficulties. Another advantage is that there is no need to divide any muscles by this procedure, because it is important to avoid injury of any collateral vessels. However, exposure of the above-the-knee popliteal artery through the posterior path of the sartorius muscle is unusual because the classical approach is through the anterior path of the sartorius muscle. The current procedure used a classic medial below-the-knee popliteal incision extended to the proximal site along the posterior edge of the semitendinosus muscle after the crural fascia was peeled carefully from the surface of the medial head of the gastrocnemius muscle to expose the medial sural artery surrounded by a venous plexus passing into the medial head of gastrocnemius muscle. Though a longer below-the-knee incision was needed in comparison to the approach reported by Barral et al., the current procedure made it relatively easy to evaluate the orientation and was an acceptable procedure indeed for surgeons with little experience with perigeniculate artery bypass.

The collateral artery originally has a small diameter that increases in size with time to replace the occluded main arterial tree, but the wall seemed relatively thin in the current case. Regular vascular clamps could easily damage this fragile vascular wall. Therefore, a pneumatic tourniquet was used to control the bleeding during the distal anastomosis. A pneumatic tourniquet substitutes for vascular clamps to preserve the integrity of the vessel because it gently and firmly occluded the arteries. It is also useful in the collateral artery bypass because it provides an unhindered operative field.

There are only few previous reports of sural artery bypasses, so the efficacy of this bypass still remains uncertain. We had no way to predict the efficiency of the bypass preoperatively. Skin perfusion pressure (SPP) is one of the useful tools for evaluating outcome of ischemic foot ulcer with conservative therapy, as Urabe et al. reported.[10] It seemed that SPP may be one of the assisted predictors of quality of the perfusion of the sural artery bypass before the ulcer recurrence. Barral et al. reported that bypass to a perigeniculate vessel alone may not be sufficient to allow tissue healing in the patient with extensive foot necrosis,[2] and such patients may require a more distal bypass to achieve limb salvage. However, the perigenicular artery bypass can be a valid option for limb salvage in selected patients with no calcification in the diseased arteries.

## CONCLUSION

This report presented a case of a successful sural artery bypass in a patient with critical limb ischemia due to Buerger's disease. A sural artery bypass is a treatment option for critical limb ischemia in selected patients with minimal arterial calcification, particularly those who are poor candidates for conventional surgical or endovascular revascularization.

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**Case Report**

# A Case Report of Aneuysmectomy after Thrombo-Intimectomy for Spontaneous Isolated Superior Mesenteric Artery Dissection

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**A 53 year-old man was admitted with acute onset of severe abdominal pain, and we performed emergent thrombectomy and intimectomy for acute, complete occlusion of superior mesenteric artery (SMA) due to its spontaneous dissection. However, 4 months later the operated part of the SMA enlarged due to aneurysm and the patient was treated by aneuysmectomy and iliac-mesenteric bypass using a saphenous vein. Aggressive treatment such as surgical or endovascular procedure is necessary for severe ischemia due to SMA dissection.**

***Keywords:*** dissection, superior mesenteric artery, surgery

## INTRODUCTION

Isolated superior mesenteric artery (SMA) dissection without an aortic dissection is a rare disorder. However, which among visceral artery dissections, it is the most common.[1] Early diagnosis of this disease has become relatively easy due to advances in imaging modalities. There is no well-established management protocol for SMA dissection.

Herein we describe a patient who was treated by surgical procedure.

## CASE REPORT

A 53 year-old man went to another institute with a 3-hour history of severe epigastric and periumbilical pain. Abdominal CT was performed and then he was transported to our institute with diagnosis of acute abdomen. On examination, he had a temperature of 37.2°C, blood pressure 146/70 mmHg heart rate of 116/min with regular rhythm. His abdomen was slightly distended with strong epigastric tenderness and slight muscular defense. The laboratory data revealed no anemia, no increase of hepatic transaminase and no acidosis of blood gas. A contrast-enhanced CT scan revealed the dissection of the SMA starting approximately 2 cm from the origin and extending about 4–5 cm, resulting in almost complete obstruction of the arterial lumen (**Fig. 1**). We diagnosed acute obstruction of SMA due to SMA dissection and judged the necessity of emergent surgery.

A median abdominal incision was made, and laparotomy was done. There were slight serous ascites and the small intestine showed moderate thickening. There was no visible peristalsis. Pulsation of the SMA was not palpable at the branching of middle colic artery. A transverse incision was made The SMA was filled with fresh thrombus and had a dissection flap. Thrombectomy using a 3 Fr Fogarty catheter and intimectomy were performed. The antegrade pulsatile blood flow was obtained, and the arterectomy was repaired directly by a running suture of 6-0 polypropylene. The arteries of intestines could be confirmed pulsation and those colors improved.

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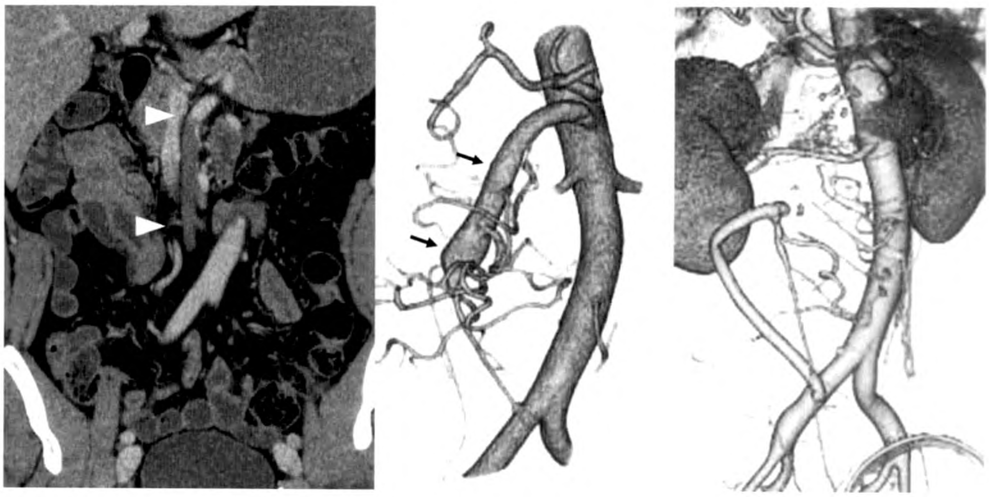

**Fig. 1** CT scan of the superior mesenteric dissection.
Left: the SMA was occluded due to the dissection (white triangle); center: 3D view showed the enlarged SMA (black arrow) at 4 months later after the 1st operation; right: CT showed ilio-ileal artery bypass after the 2nd operation.
SMA: superior mesenteric artery

We judged that the ischemia was recovered and did not add other procedures to the intestines. The patient was started oral intake from the 5th post-operative day and discharged without complications.

However, the follow up CT four months later showed that his SMA was dilated, and we made the decision to reoperate. Contrast CT revealed that the SMA was 30 mm in diameter with thickened wall and dissection between about 3 cm from aortic origin and the distal part. We thought that there was a risk of rupture. The reoperation was done by median incision, and careful exfoliation was performed because of severe adhesion. The SMA was exposed from the origin to the whole aneurysm with the branches. The SMA had no communication with the inferior pancreaticoduodenal artery but had branches of a middle colic artery, a right colic artery, an ileocolic artery and two ileal arteries. After heparinization, the ostium of the SMA was doubly ligated, the dilated SMA was opened. The aneurysmal wall was found to be thickened. The middle colic artery, the right colic artery and the ileocolic artery, which were slender and had good back flow, were occluded by suture ligation. The two ileal arteries were bypassed using saphenous vein from the right common iliac artery. The excised aneurysmal wall histologically showed myxomatous change and destruction of the media, which were suspected of cystic medial necrosis (**Fig. 2**) After the operation the patient suffered from complications of paralytic ileus. However, his condition improved, and he was discharged.

## Discussion

Isolated dissection of abdominal visceral artery without an aortic dissection is relatively rare.[2] Among such dissections, SMA dissection is the most frequent[1,2] and more frequently detected due to the increasing use of CT.[3] The pathogenesis of SMA dissection has been not resolved, but its relationship with hypertension, smoking, trauma, cystic medial necrosis, fibromuscular dysplasia, atherosclerosis, vasculitis, connective tissue disease and segmental mediolytic arteriopathy has been investigated. This patient smoked, and the histopathological findings suggested cystic medial necrosis of the SMA. The natural course of SMA dissection would include limited progress with cessation, progressive involvement of the vessel, reestablishment of flow into the true lumen, or rupture through the adventitia.[2]

Various treatments have been applied to SMA dissection. Therapeutic procedures include conservative, medical, endovascular and surgical treatments. Original conservative treatment consisted of bowel rest and observation. One review found that conservative treatment was successful in 31 of 56 patients (55%).[4] Medical treatment includes antiplatelets, anticoagulant, antihypertensive drugs, anti-inflammatory drugs and steroid.[5] At first, medical treatment with or without anticoagulation agent is recommended for SMA dissection where there is no evidence of bowel ischemia. Successful recovery by medical treatment was reported at 55%–63%.[4,6,7] However,

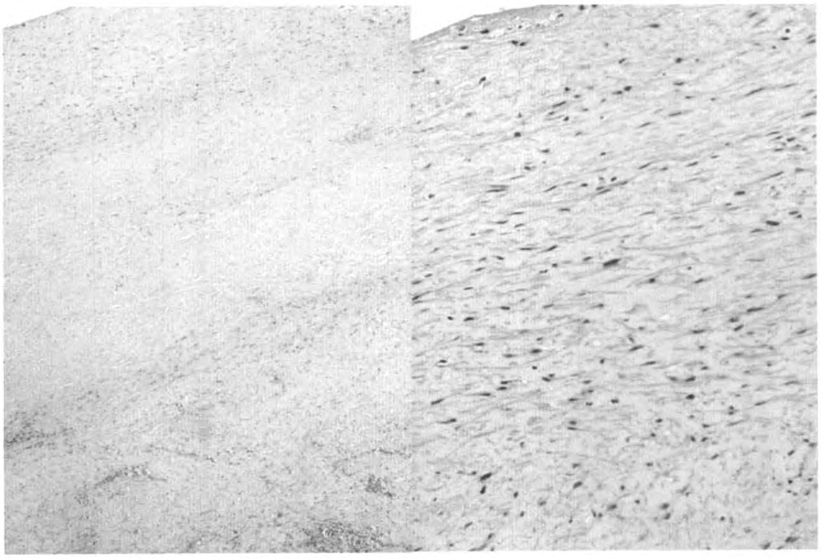

**Fig. 2** Histopathology of SMA wall.
The excised specimen revealed that arterial wall structure was destructed with myxomatous degeneration and gathering of macrophages. (Hematoxilin-Eosin staining, left: × 50; right: × 200)
SMA: superior mesenteric artery

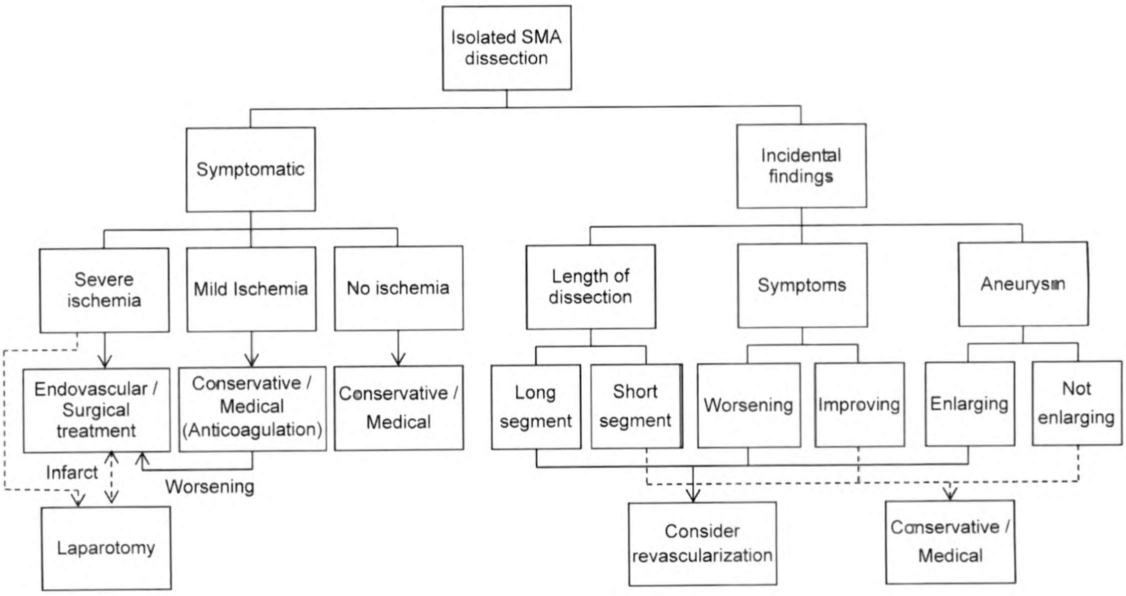

**Fig. 3** Algorithm for management of spontaneous SMA dissection.
SMA: superior mesenteric artery

medical treatment will fail in over one third of the cases of SMA dissection and require further intervention.[6] Physicians should consider that treatment may fail to prevent the progression of bowel ischemia and aneurysmal dilatation (**Fig. 3**). It is not easy to diagnose the bowel ischemia which needs revascularization. Subhas et al.[2] advocated the management algorithm and recommended diagnostic laparoscopy. In a severe case, closed observation is necessary and intensive care including surgical treatment with lapatoromy should be considered without hesitation. In such cases, a less invasive treatment is preferred, and endovascular management of stent placement or balloon angioplasty is selected for SMA dissection.4,7) Most of reported patients with endovascular treatment showed good results, although the follow-up periods have been short. Surgical procedures have been variously reported, including thrombectomy, endoaneurysmorrhaphy, intimectomy, ligation, resection, and bypass surgery. Operative revascularization is indicated when there are signs and symptoms of intestinal ischemia, progression of dissection or aneurysm, narrowing of the true lumen/thrombosis of true lumen or saccular aneurysm formation that is likely to rupture or embolize.2) Absolute surgical indications are arterial rupture and intestinal infarction. Intestinal resection may be required if ischemic necrosis is present. At the first operation we performed emergent thrombectomy and intimectomy because of severe symptoms and abdominal findings. Subsequently, the SMA enlarged and changed into an aneurysm due to the wall weakness or due to the surgical effect of thrombectomy. Because the reported surgical cases of SMA dissection were few, the long-term results of surgical techniques and the complications are not clear. We should select the surgical procedures and should follow up the clinical course in consideration of such complications.

Sakamoto et al. categorized SMA dissection into four types: type I, patent false lumen with both entry and re-entry; type II, 'cul-de-sac' shaped false lumen without re-entry; type III, thrombosed false lumen with ulcer-like projection (ULP); and type IV, completely thrombosed false lumen without ULP.8) Sakamoto reported that one patient with type II needed urgent surgery because of small bowel ischemia and 11 other patients were treated conservatively. Zerbib et al.9) proposed a modified classification: type I – IV of Sakamoto's classification; type V, aneurysmal dissection with stenosis of the distal part of the SMA; and type VI, total [VIa] or partial [VIb] thrombosis of the SMA. Most patients of type I respond to conservative treatment but need long time follow-up. Zerbib recommended that intervention should be considered in types II, III, V, and VI, when there are dissecting aneurysms at least 2 cm in diameter, or stenosis over than 70%.9) And some algorithms for management of SMA dissection are advocated.2,4,6) Our patient belonged to type VIa and the CT revealed long segment obstruction at the onset.

Because of an increasing trend to use CT scanning due to improvement of CT resolution,10) most of the cases reported are within the last ten years.9) We experienced ten patients with SMA dissection during the past 7 years. Among the ten there was no intervention due to risk of rupture at acute or subacute onset periods. There was another one patient received endovascular treatment due to the SMA occlusion except this case. The treatment should be decided according to the symptoms, signs and the dissection configuration.

## Conclusion

We report a rare case of isolated SMA dissection, which was treated by surgical procedure. Thrombectomy with intimectomy were first performed. Four months later anerysmectomy and mesenteric bypass were done for the dilated SMA. Surgery or endovascular treatments are indicated when symptoms are acute and there is suspicion of. mesenteric ischemia.

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**Case Report**

# Mycotic Celiac Artery Aneurysm Following Infective Endocarditis: Successful Treatment Using N-butyl Cyanoacrylate with Embolization Coils

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**Mycotic celiac artery aneurysm following infective endocarditis is extremely rare and, to our knowledge, only four cases have been reported in the literature to date. We describe the case of a 60 year-old man who developed a mycotic aneurysm of the celiac artery, which was detected by computed tomography (CT) following an episode of infective endocarditis. He successfully underwent endovascular isolation and packing of the aneurysm using N-butyl cyanoacrylate (NBCA) with embolization coils.**

***Keywords:*** mycotic celiac artery aneurysm, embolization, n-butyl cyanoacrylate

## INTRODUCTION

Aneurysm of the celiac artery accounts for 4% of all visceral artery aneurysms (VAA).[1)] Mycotic celiac artery aneurysm is extremely rare and, to our knowledge, only four cases have been reported in the literature to date.[3–6)] We present a case of mycotic celiac artery aneurysm following an episode of infectious endocarditis. The aneurysm was detected on computed tomography (CT) and successfully treated by endovascular therapy using N-butyl cyanoacrylate (NBCA) with embolization coils.

## CASE REPORT

A 60 year-old man who was a healthy and had no previous diseases. The patient was referred to our hospital with a history of persistent fever since four months developed a headache, in addition to the fever. Cranial magnetic resonance imaging (MRI) revealed chronic, multiple cerebellar infarcts. Blood tests performed on admission revealed a high white blood cell counts (14000/μl; normal, <9000/μl) and high C-reactive protein levels(5.767 mg/dl; normal, <0.5 mg/dl). The patient was diagnosed with infective endocarditis on the basis of echocardiographic findings, which revealed vegetation in the anterior mitral leaflet and aortic valve. Initial CT scans performed on admission did not reveal any abnormal findings (**Fig. 1A**). Blood culture revealed the presence of *Streptococcus*; consequently, a course of antibiotics (ampicillin+gentamicin) was initiated. On the seventh day after admission, the patient complained of abdominal pain. An abdominal X-ray indicated ileus and blood tests revealed mildly elevated liver function; however, abdominal ultrasound imaging showed no abnormal findings. Hazy mesenteric fat around the celiac artery was observed on CT images (**Fig. 1B**), which was later identified as the first sign of inflammation. The ileus improved with conservative treatment.

On the thirteenth day after admission, aortic and mitral valve replacement surgery was performed. Aortic valve was replaced by mechanical valve (CarboMedics Top Hat valve, 23 mm, CarboMedics, Inc., Austin, TX, USA). Mitral valve

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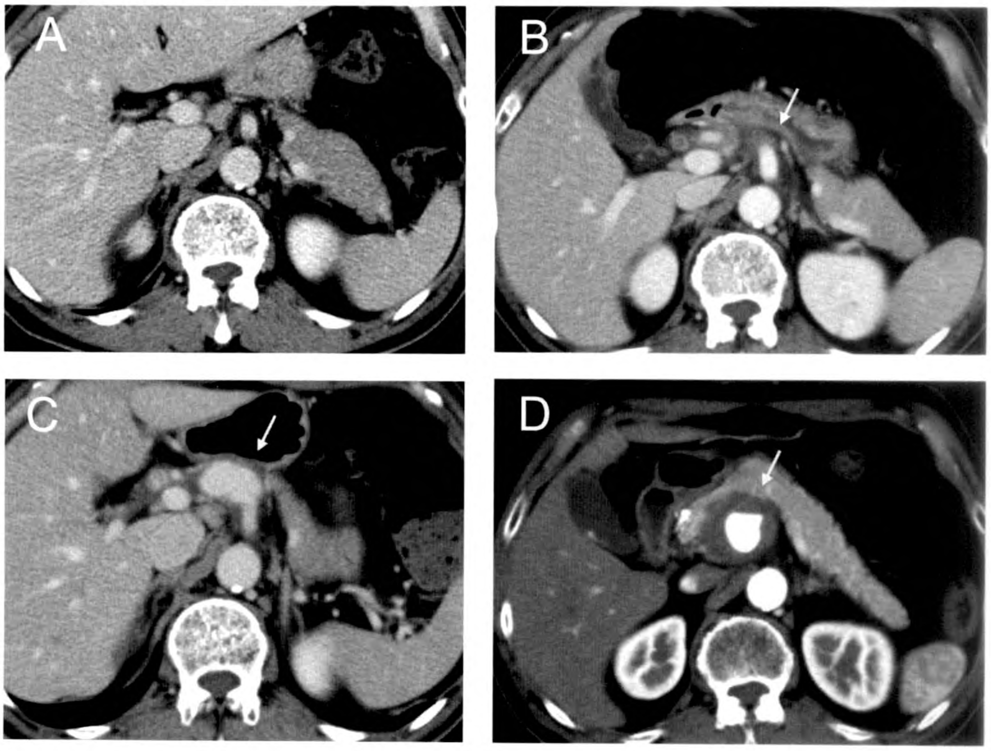

**Fig. 1** Computed tomography imaging.
**A**: Computed tomography imaging at the time of hospitalization. There are no abnormal findings. **B**: Seventh day after hospitalization. Hazy fat density is observed around the celiac artery (arrow). **C**: Thirtieth day after hospitalization. A celiac artery aneurysm (arrow) with a diameter of 17 mm is observed. **D**: Nine months after hospitalization. Expansion of the celiac artery aneurysm (from17 mm to 50 mm) is observed. The aneurysm was suspected a pseudoaneurysm, and there is sever adhesion among surrounding tissues.

was also replaced mechanical valve (CarboMedics standard mitral valve, 25 mm, CarboMedics, Inc., Austin, Tx, USA). The cultures of those valves were negative.

CT imaging prior to surgery revealed an aneurysm of approximately 17 mm in diameter in the celiac artery (**Fig. 1C**). Although the clinical course of the patient indicated the diagnosis of a mycotic aneurysm, we decided to keep the patient under strict observation. The patients was given antibiotics via an intravenous route for two weeks following valve replacement surgery and wasswitched to an oral route thereafter. Postoperative CT imaging was performed at regular intervals, but no change was observed in the size of the aneurysm. His postoperative course was uneventful, and he was discharged on the sixteenth postoperative day.

A CT scan (**Fig. 1D**) performed eight months after valve replacement surgery (9 months after admission) revealed a sudden enlargement of the aneurysm (from 17 mm to 50 mm), leading to the suspicion of a pseudoaneurysm (**Fig. 2**). He had no symptoms and no fever. Blood tests performed on admission revealed a normal white blood cell counts (6300/μl; normal, <9000/μl) and normal C-reactive protein levels(0.57 mg/dl; normal, <0.5 mg/dl). The aneurysm was large enough to alter the shape of the pancreas. We suspected the pseudoaneurysm. There is the sever adhesion among the celiac artery aneurysm and surrounding tissues. (**Fig. 1D**). Because he took Warfarin and Aspirin, he had a greater risk of bleeding. We thought open surgical repairs were difficult. Therefore, endovascular embolization was attempted using an approach via the right femoral artery. There were no abnormalities in the superior mesenteric artery (SMA) and portal vein. Celiac angiography revealed a fusiform aneurysm in the trunk of the celiac artery and a pseudoaneurysm located below it (**Fig. 3A**). The common hepatic and splenic arteries diverged at the fusiform aneurysm, and the left gastric artery branched off the celiac artery from the proximal side of the aneurysm (**Fig. 3A**).

First, we performed the embolization of the common hepatic artery using an interlocking detachable coil

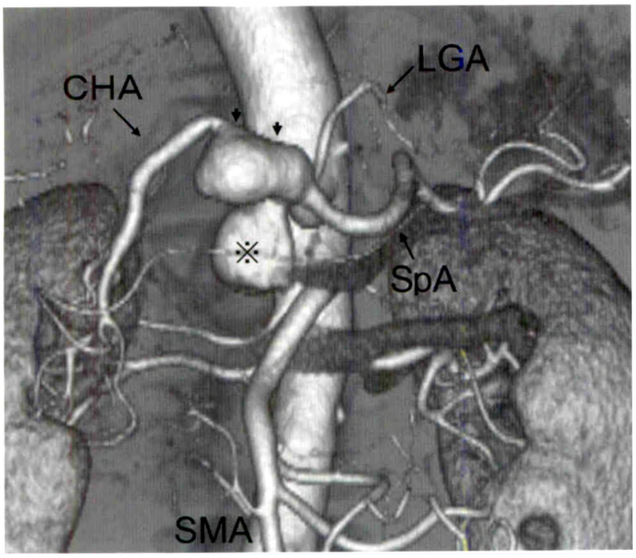

**Fig. 2** Three-dimensional computed tomography nine months after hospitalization
Three-dimensional computed tomography reveals a celiac artery aneurysm (arrow head) and a pseudoaneurysm located below it (※).
CHA: common hepatic artery; LGA: left gastric artery; SpA: splenic artery; SMA: superior mesenteric artery

system (IDC system; Boston Scientific Corp., Massachusetts, USA) and fibered IDC system (Boston Scientific Corp.). Similarly, selective embolization of the splenic artery was performed using the IDC system. For tight packing of the aneurysm, we injected iodized oil (Lipiodol; Guerbet, Aulnay-sous-Bois, France) and NBCA (Histoacryl; B.Braun Melsungen AG, Melsungen, Germany) in a 1:1 ratio into a nest of detachable coils(Cook Medical, Indiana, USA) in the celiac axis under temporary balloon occlusion (3.3F; Fuji Systems Corporation, Tokyo, Japan) to prevent glue migration. Finally, embolization of the celiac axis distal to the left gastric artery was performed using the fibered IDC system, and isolation and packing of the whole aneurysm was completed (**Fig. 3B**). Postoperatively, normal perfusion to the liver and spleen via a collateral circulation was observed; in addition, there were no postoperative complications. Follow-up MRI revealed shrinkage of the aneurysm; moreover, there was no recurrent infection or recanalization of the aneurysm twelve months after the embolization procedure.

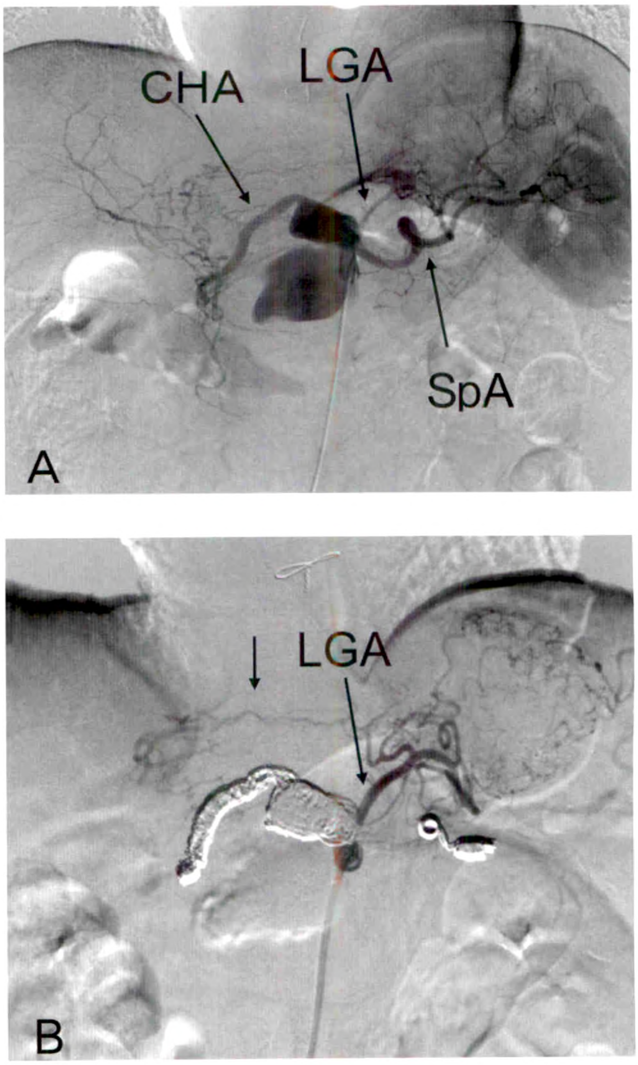

**Fig. 3**
**A**: Primary selective angiography of the celiac trunk.
**B**: After isolation and packing of the aneurysm, collaterals to the liver (arrow) and the spleen via the patent left gastric artery are identified.
CHA: common hepatic artery; LGA: left gastric artery; SpA: splenic artery

## DISCUSSION

Celiac artery aneurysms, which account for approximately 4% of all VAAs,[1] may extend to involve the major branches of the celiac artery to varying degrees.[2] Mycotic aneurysms, on the other hand, tend to be multiple, with the most common site of involvement being the femoral artery. However, most mycotic VAAs occur in SMA.[4,6] Mycotic celiac artery aneurysm due to infective endocarditis is extremely rare, and, to our knowledge, only four cases have been reported in the literature to date. (Sweany, 1919; Zeppa, 1966; Jatene, 1990; and Dor 1993)[3–6]

Celiac artery aneurysms presumably arise as a result of arteriosclerosis and medial degeneration; however, trauma, dissection, and Takayasu arteritis can also be causes.[2] Because our patient had a medical history of infective endocarditis, we deduced that he developed a pseudoaneurysm subsequent to inflammation of the visceral wall, which was induced by septic emboli.

Early recognition and accurate characterization of this vascular anomaly are essential because the operative mortality rate increases from approximately 5% to 40% if the aneurysm ruptures during surgical intervention.[7] Because of the rarity of these aneurysms, their natural history is poorly understood. Criteria for intervention in asymptomatic patients should include the following: aneurysms >2 cm in diameter with reasonable operative risk, radiologic evidence of increasing aneurysm size, or size >3–4 times the original diameter of the vessel (8 mm).[7]

Even so, a mycotic celiac artery aneurysm that ruptured on attaining a size of 1.5 cm has been reported.[2] However, these were small studies; as a consequence, no strict size criterion has been identified as a risk for rupture. In our case, the earliest CT finding **(Fig. 1)** was that of hazy mesenteric fat around the celiac artery. Retrospectively, we believe this hazy mesenteric fat be the first sign of inflammation.[8] Thus, we advocate frequent CT scanning to check for the appearance of hazy mesenteric fat around visceral arteries and to evaluate the possible formation of VAA.

Treatment options for VAA include conventional open surgery and less invasive catheter-based techniques. Several reports document low morbidity and mortality rates with endovascular intervention for VAA, with technical success rates reportedly ranging from 75% to 100%.[9] Saltzberg et al.[9] recommended endovascular repair as a first line of treatment for VAAs in anatomically suitable cases, excluding those with lesions located in the distal splenic artery. Endovascular techniques confer many possible advantages: anatomic localization; ability to perform with local anesthesia; easy assessment of collateral circulation; decreased postoperative complications including ileus obstruction, abscess, bleeding, wound infection, and pancreatitis; and shorter hospital stays. However, complications of coil embolization include end organ infarction, sacrifice of the visceral vessel aneurysm recurrence, abscess, arterial disruption, contrast-induced acute kidney injury, pain, fever, embolism, infarction, and access site hematomas.[7] Occlusion of the celiac trunk should be avoided if the portal vein or SMA are not patent or in cases of liver dysfunction. Occlusion of the gastroduodenal artery also presents a relative contraindication.[10]

According to classical surgical considerations, implantation of prosthetic material in an infected environment could hamper a favorable long-term outcome. However, endovascular treatment with appropriate antibiotic therapy can also be a definitive line of treatment, with the advantages of reduced invasiveness in patients with extensive comorbidities. However, regular follow-ups with blood analysis and ultrasonography to check for additional aneurysm formation due to recurrent infection is mandatory after endovascular treatment.

In this case, we were able to safely perform distal embolization with packing within the aneurysmal sac and proximal embolization of the celiac axis. Packing of the aneurysm, using both coils and NBCA, was extremely effective in terms of cost and procedure time. Moreover, it is safer to use NBCA with coils because it tends to aggregate in the coil nest. In addition, decreased blood flow under temporary balloon occlusion prevents the distal embolization of glue. This combination decreases the amount of NBCA injected and the number of expensive coils delivered around the aneurysm. Limiting the number of coils delivered into the aneurysm is also important to reduce the risk of periprocedural aneurysm rupture due to enlargement of the aneurysm.[11]

An important potential risk of endovascular treatment is postoperative recanalization or regrowth of the aneurysm. However, because artifacts from the metallic coils disrupt postoperative CT surveillance,[2] long-term follow up may require duplex ultrasonography, MRI/angiography, or conventional, digital subtraction angiography.

Endovascular treatment of celiac artery aneurysms is now recognized as a relatively safe and effective method, even for mycotic aneurysms. In future, randomized controlled studies with long-term follow-up after endovascular treatment should be considered to establish the indications for endovascular treatment as an alternative to surgical intervention.

## CONCLUSION

Few reports exist on the clinical course of mycotic celiac artery aneurysms. The initial CT sign of a mycotic aneurysm is a hazy fat density, which is indicative of fat in the periarterial tissue. Periodic follow-up CT imaging should be performed at short intervals, in addition to a strict antibiotic regimen, when this finding is detected on initial CT. If the aneurysm appears to be expanding, treatment must be promptly initiated irrespective of size. In this case, endovascular therapy was both effective and safe. Strict follow-up observations are necessary to reduce the possibility of recurrent infection, which may lead to the formation of additional aneurysms.

## DISCLOSURE STATEMENT

The authors disclose no conflicts of interest.

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**Case Report**

# Congenital Systemic-Pulmonary Collateral Vein Unexpectedly Noticed after Central Venous Catheter Insertion

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**Congenital systemic-pulmonary collateral vein (i.e. levoatriocardinal vein) is an uncommon cardiac anomaly. We report a rare case of congenital systemic-pulmonary collateral vein incidentally noticed after accidental migration of a central venous catheter. Cardiac CT showed the vertical vein connected to the left upper pulmonary vein (LUPV) and another thin abnormal vessel was shown running caudally from the LUPV, connecting to the coronary sinus. Furthermore, the normal connection between the LUPV and the left atrium remained. There were two levoatriocardinal veins from the LUPV without atrial egress failure. To our knowledge, this might be the first report of such a case.**

***Keywords:*** central venous catheter, migration, congenital systemic-pulmonary collateral vein

## INTRODUCTION

Central venous (CV) catheters are frequently used for administration of chemotherapeutic agents, parental nutrition, and vascular access. Various complications have been reported in the literature,[1)] with migration being a major complication. We report a case of migration of the CV catheter tip into the congenital systemic-pulmonary collateral vein.

## CASE REPORT

A 66 year-old woman who had non-viral liver cirrhosis was admitted to our hospital for liver transplantation. She had massive ascites and pyelonephritis and had been treated with antibiotics for a few weeks. A CV catheter was inserted into the left internal jugular vein by bedside. A chest radiograph after the procedure showed the CV catheter tip was located in the left side of the chest (**Fig. 1**), which led us to suspect migration to unexpected vein instead of the superior vena cava (SVC). We reviewed previous chest computed tomography (CT) images, which showed a small vein running lateral to the aortic arch, presenting as the vertical vein. Existence of an abnormal connection between the vertical vein and the left upper pulmonary vein (LUPV) was suspected. Venography obtained while contrast material was injected from the CV catheter showed the vertical vein, followed by the LUPV, the left atrium (LA), the left ventricle (LV) and the ascending aorta (**Fig. 2**). In addition, it showed the innominate vein (i.e. left brachiocephalic vein) and the superior vena cava (SVC) following the vertical vein. Furthermore, another small vessel that was running caudally from the LUPV was observed. At this time, we could not understand the detailed anatomy. However, we feared that complications, such as brain infarction and arterial embolism, might occur if the CV catheter were left in this position. Hence, we inserted a CV catheter from the right subclavian vein under ultrasonographic guidance,

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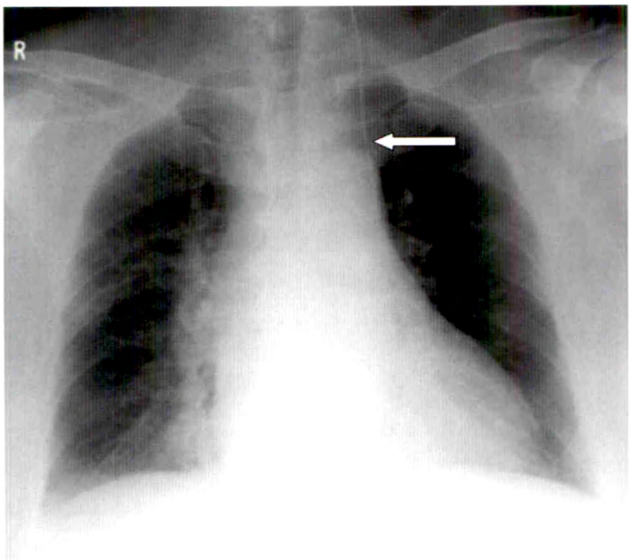

**Fig. 1** Chest radiograph after the procedure.
The central venous catheter tip is located in the left side of the chest (arrow).

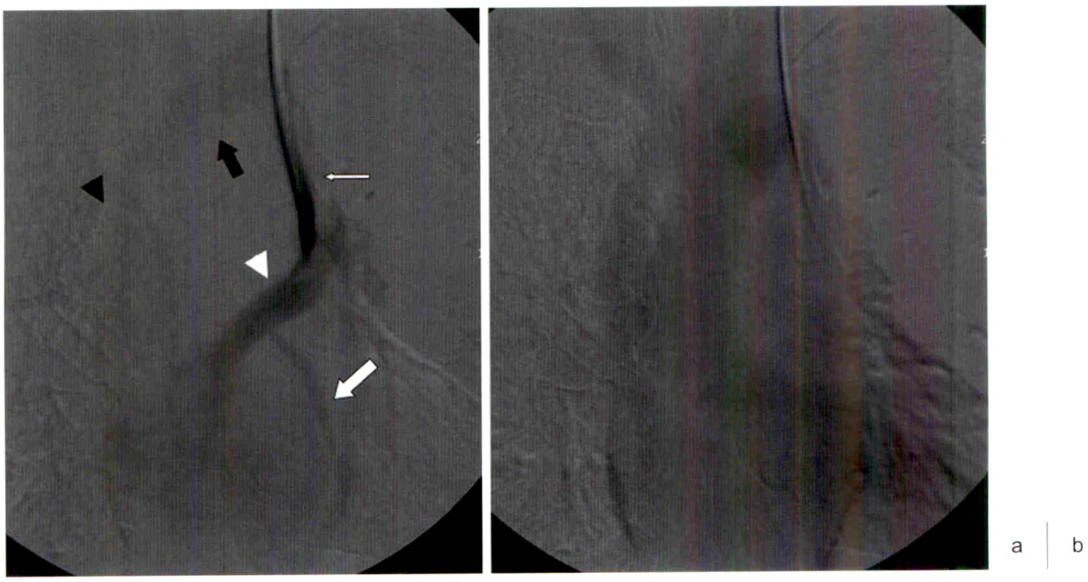

**Fig. 2** Venography obtained while contrast material was injected from the central venous catheter.
**a**: Early phase.
The vertical vein (narrow white arrow) is shown, which is followed by the left upper pulmonary vein (large white arrowhead) and the left atrium. Another small vessel (wide white arrow) is running caudally from the left upper pulmonary vein. In addition, the innominate vein (black arrow) and the right superior vena cava (black arrowhead) are shown.
**b**: Late phase.
The left ventricle and the ascending aorta are shown, consecutively.

and indwelled it at the SVC with X-ray fluoroscopy, and removed the CV catheter previously inserted at the vertical vein.

To evaluate the precise anatomy of abnormal vessels, a contrast-enhanced cardiac multi-detector row CT examination was performed. According to these CT images, the vertical vein was shown to be connected to the LUPV. The normal connection between the LUPV and the LA remained, and another small vessel arising from the LUPV was shown running caudally. This small vein was connected to the coronary sinus and drained into the right atrium (RA) (**Fig. 3**).

In a summary obtained from various radiographic images, the vertical vein and the small vessel also was revealed as congenital systemic-pulmonary collateral veins. The direction of blood flow was considered from the LUPV to the vertical vein, draining to the RA via the innominate vein. Other than this abnormal connection, the direction of blood flow of the small vessel was observed from the LUPV to the coronary sinus, draining to the RA. These results indicated that the hemodynamics was a left-to-right shunt.

Echocardiography showed Qp/Qs was 0.85 with no right ventricular failure. Arterial blood gas analysis showed no cyanosis. No risks for liver transplantation were detected, and, therefore, the operation was performed without any problems.

## DISCUSSION

Pulmonary blood flow to the systemic vein occurs with partial anomalous pulmonary venous connection (PAPVC), in which the normal connection between the pulmonary vein (PV) and LA usually disappears. The connection between the PV and systemic veins with normal drainage to the LA has been named congenital systemic-pulmonary collateral vein. Congenital systemic-pulmonary collateral vein is a rare venous anomaly, first reported by McIntosh in 1926.[2)]

In the early stage of fetal development, peripheral pulmonary veins develop from the capillary plexus surrounding the embryonic foregut, forming the main pulmonary vein, and finally connecting the LA.[3)] At first, the capillary network anastomoses to the cardinal, umbilical and vitelline veins. During this development, anastomoses between the pulmonary and systemic veins disappear. Sometimes peripheral pulmonary veins connect the cardinal veins instead of the LA. This is called total anomalous pulmonary venous connection (TAPVC) or PAPVC, depending on whether there is complete or partial pulmonary venous connection failure, respectively. Rarely, although the connection between the PV and the LA is formed normally, pulmonary venous drainage fails within the heart. The embryonic pulmonary systemic venous anastomosis remains and forms a congenital pulmonary systemic collateral vein. This resulting anastomosis is called levoatriocardinal vein.[4)] Most cases of levoatriocardinal vein connect LA to derivatives of cardinal veins or their tributaries, instances of the SVC or the innominate vein.

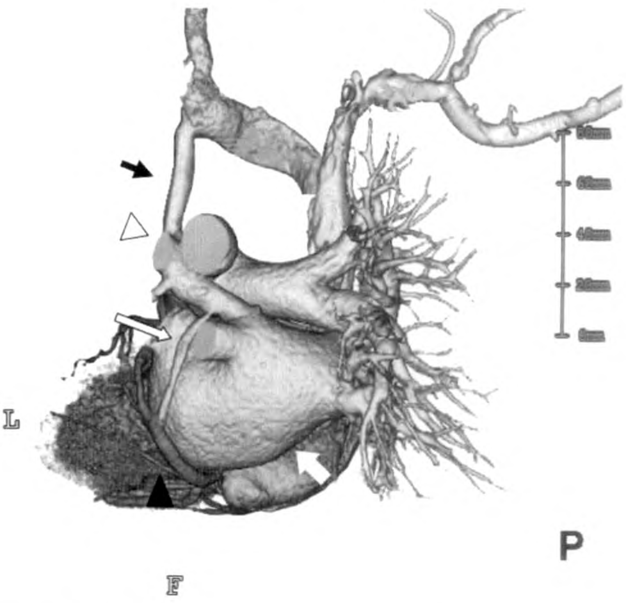

**Fig. 3** Posterior view of three-dimensional image of heart by computed tomography.
The vertical vein (black arrow) is connected to the left upper pulmonary vein (white arrowhead). A normal connection between the left upper pulmonary vein and the left atrium (wide white arrow) remains, and another small vein (narrow white arrow) arising from the left upper pulmonary vein is shown running caudally. This small vein is connected to the coronary sinus (black arrowhead), draining into the right atrium.

Most cases of levoatriocardinal vein have left atrial egress failure including multiple levels of obstruction to left-sided outflow, such as mitral atresia, aortic atresia and coarctation.[5–8)] However, 8 cases were reported without left atrial egress.[6)] Moreover, 3 cases without other cardiac anomalies were reported, found by angiogram or MRI incidentally, as in the current case.[5,8,9)] In most cases, there are no clinical symptoms caused by levoatriocardinal vein itself.

The levoatriocardinal vein should be considered different from the left superior vena cava (LSVC).[8)] Usually, the LSVC connects to the RA through the coronary sinus. In the early embryonic stage, there is a symmetrical precardinal vein system, and the left precardinal vein disappears. LSVC occurs when the left precardinal vein remains.[10)] Fujiwara described the levoatriocardinal vein mimicking the LSVC, running dorsal of the LUPV.[7)] Haris reported a patient with both the levoatriocardinal vein and the LSVC draining to the coronary sinus normally.[10)] These are ways to distinguish the LSVC and the levoatriocardinal vein. In the present case, although the vertical vein was similar to the LSVC, the normal connection to the coronary sinus was missed, which led to misidentifying the vertical vein as the LSVC. Meanwhile, there was an additional connection between the LUPV and the coronary sinus. Levoatriocardinal vein has various types of connection in literatures.[8)] Levoatriocarcinal vein is defined as connection between PV or LA to systemic vein such as SVC, internal jugular vein and innominate vein. Besides coronary sinus is one of systemic vein, which arises from the left common cardinal vein, this additional connection was regarded as another levoatriocardinal vein. In summary, two levoatriocardinal veins from the LUPV without atrial egress failure were observed in this case. When a CV catheter is inserted, we should be aware of rare, abnormal anatomy, in addition to complications of puncture, such as pneumothorax and hemothorax.[11)]

## CONCLUSION

This is a rare case of migration of the CV catheter tip into a congenital venous anomaly. To our knowledge, this might be the first report of such a case.

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**Case Report**

# Endovascular Management of May-Thurner Syndrome

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**May-Thurner syndrome or iliac vein compression syndrome is associated with deep vein thrombosis (DVT) resulting from chronic compression of the left iliac vein against lumbar vertebrae by the overlying right common iliac artery. Historically, May-Thurner syndrome has been treated with anticoagulation therapy. However, this therapy can be problematic when given alone, because it prevents the propagation of the thrombus without eliminating the existing clot. Furthermore, it does not treat the underlying mechanical compression. Consequently, syndrome who was managed by anticoagulation therapy alone, there is a significant chance that the patient will develop recurrent deep vein thrombosis or post thrombotic syndrome or both. Recently, both retrospective and prospective studies have suggested that endovascular management should be front-line treatment; endovascular management actively treats both the mechanical compression with stent placement and the thrombus burden with chemical dissolution. We report our case of 53 years old male patient with May Thurner syndrome who managed by endovascular treatment.**

***Keywords:*** may-thurner syndrome, iliac vein compression syndrome

## INTRODUCTION

In 1957, May and Thurner described three varieties of intra-luminal spurs occurring in the left common iliac vein close to its junction with the inferior vena cava (IVC).[1] The incidence of May-Thurner syndrome is unknown and ranges from 18%–49% among patients with left-sided lower extremity DVT.[2] May and Thurner postulated that the chronic pulsations of the overriding right iliac artery led to the development of a "spur" in the vein wall and that this spur would result in partial venous obstruction, Chronic trauma to the inner side of the vein wall due to adjacent arterial pulsations leads to the accumulation of elastin and collagen, contributing to spur formation.[3] In addition to the chronic arterial pulsations, mechanic compression of the iliac vein by the thick-walled overriding iliac artery (**Fig. 1**) leads to extensive local intimal proliferation, impaired venous return and venous thrombosis. In addition to the mechanical alterations to the vessel wall, hypercoagulable states, when tested, are found in the majority of patients. Kolbel et al.[4] found underlying hypercoagulable disorders in 67% of patients screened prior to treatment of chronic iliac vein occlusion. Left iliac vein compression is the most common variant seen in May-Thurner syndrome; however, several other variants have been described in the literature. Compression of the left common iliac vein by the left internal iliac artery,[5] compression of the right common iliac vein by the right internal iliac artery,[6] compression of the IVC by the right common iliac artery[7] and right-sided May-Thurner syndrome in a patient with a left-sided IVC[8] have all been described.

## CASE REPORT

53 years old male with diabetes mellitus and hypertension who persistent with painless swelling of the left thigh of about 7 years duration. The swelling had gradually become more severe. Physical examination revealed a swollen left thigh, circumference of which was 15 cm larger than the right one. The patient had two episodes of venous thrombosis, and the last episode occurred 2

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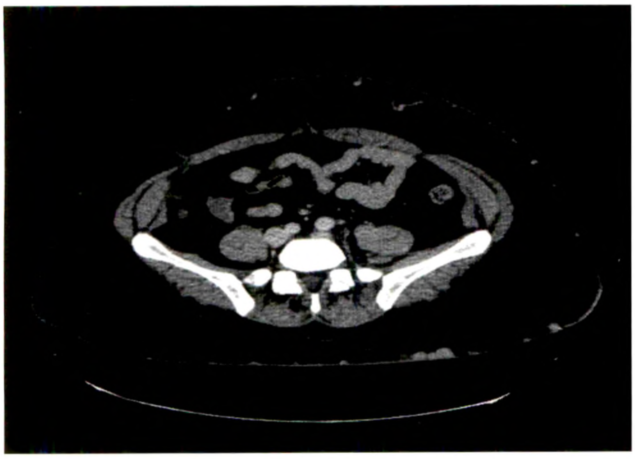

**Fig. 1** CT of the abdomen and pelvis with contrast showing compression of left iliac vein by left iliac artery, multiple collaterals seen at abdominal wall.

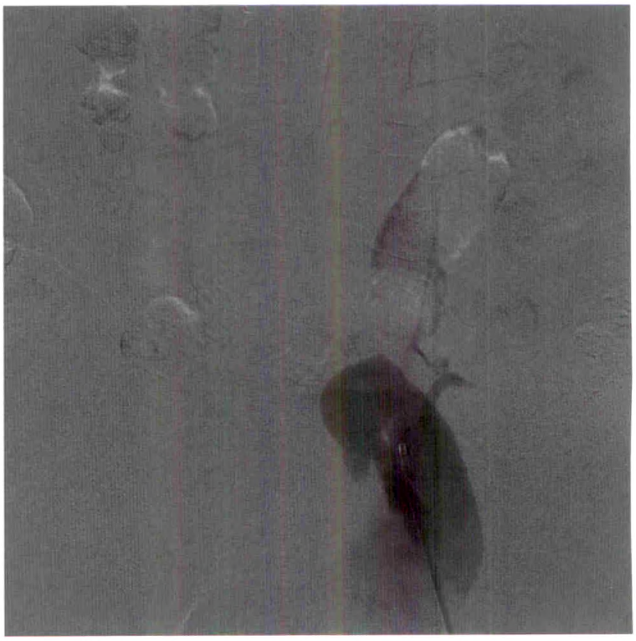

**Fig. 2** 8F sheath was placed into left common femoral vein, venogram revealed total occlusion of left common iliac vein with subsequent aneurysmal dilatation of left external iliac vein.

weeks earlier, which dramatically aggravated his symptoms. He was treated with warfarin 6 mg and aspirin 300 mg with no appreciable improvement. Venous Doppler ultrasonography (U.S.); revealed left common femoral thrombosis, occluded left common iliac vein with subsequent aneurysmal dilatation of external iliac vein. Abdominopelvic computed tomography (CT) was done with dual-phase thin-section (section thickness, 1.25 mm). Abdominal CT was performed at arterial (angiography) and venous (venography) phases with four-channel multi–detector row CT. Three-dimensional volume rendering and abdominal CT demonstrated normal arterial anatomy and compression of the left common iliac vein by the left common iliac artery with total occlusion of the common iliac vein, aneurysmal dilatation of left external iliac vein with multiple collaterals seen along left thigh and anterior abdominal wall, as well as evident thrombosis of common femoral vein which extended down to involve superficial femoral and popliteal veins. No pelvic mass was noted. Endovascular venoplasty was decided.

A 6-F sheath was placed into the right common femoral vein; Rt iliac venography and cavogram was done followed by deployment of retrievable IVC filter just below renal vein retrievable OptEase filter (Johnson and Johnson, USA), another 8 F sheath was placed into left common femoral vein, venogram was done, and total occlusion of iliac vein was observed with subsequent aneurysmal dilatation of left external iliac vein with multiple collaterals (**Fig. 2**), micro-catheter (Renegade by Boston scientific, USA) was successfully manipulated over 0.018 wire (Transend 0.018 wire, Boston Scientific, USA) and successfully transverse through occluded segment to IVC, cavogram was done to confirm the position of micro-catheter, multiple balloon dilatation were done starting by 2 mm × 6 mm (Sleek balloon by Clear Stream Technologies) followed by 4, 6, 8, 10, and 12 × 40 mm Power flex balloon by (Johnson and Johnson,_USA). A 14 mm × 40-mm Wallstent (Boston Scientific, USA) was deployed across the occluded segment of the vein. The stent was dilated to 14 × 40 mm with the angioplasty balloon. A post-angioplasty venogram demonstrated a widely patent stent and good contrast material flow through the stent into the IVC, without filling of the cross-pelvic collaterals (**Fig. 3**). Measurement demonstrated no pressure gradient across the stent in the supine position.

While the patient was lying prone on the angiographic table, we accessed the popliteal vein under ultrasonographic (U.S.) guidance with a small-gauge echogenic needle to avoid inadvertent puncture of the adjacent popliteal artery. A 5-F sheath was inserted through which all subsequent catheter and wire exchanges were performed. Using (multi–side port catheter infusion set, Cook Medical, USA). 10 mg of tissue plasminogen activator (tPA) (actilyse, Boehringer Ingelheim, Germany) was injected through infusion catheter as a loading dose, and then infusion catheter was connected to actilyse

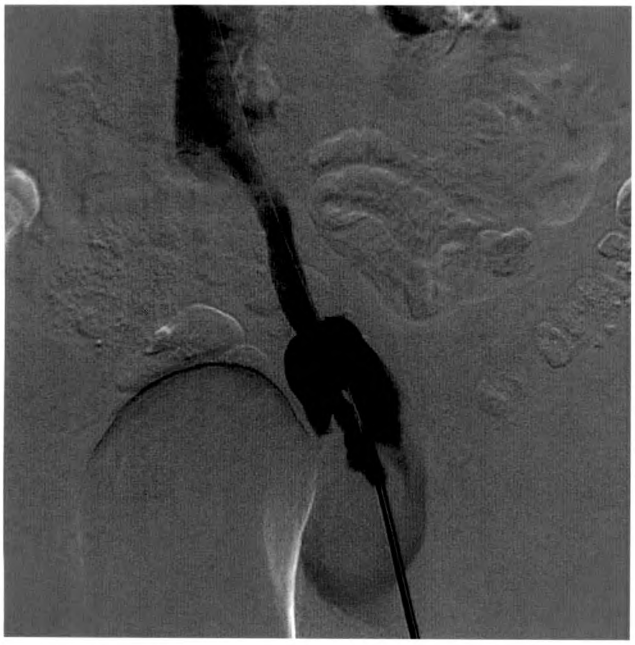

**Fig. 3** A post-angioplasty venogram demonstrated a widely patent stent and good contrast material flow through the stent into the inferior vena cava, without filling of the cross-pelvic collaterals.

infusion pump with a dose of 0.5 mg/hour, Lysis progress was monitored at venography at 8 hours interval, total lysis was achieved after 16 hours.

The patient was discharged from the hospital on the same day and prescribed the following drug regimen: warfarin 6 mg for 3 months, then 300 mg of aspirin daily for life and 75 mg of Clopidogrel (Plavix, Sanofi-Dogu, Istanbul, Turkey) daily for 6 weeks. At 2 weeks follow-up, Doppler U.S. revealed patent venous stent, and left thigh edema dramatically decreased. Then IVC filter was retrieved. At 3-month follow-up, Doppler U.S. revealed patent venous stent, and left thigh edema was substantially decreased.

## DISCUSSION

A history of persistent left lower extremity swelling with or without DVT in a woman between the 2nd and 4th decades of life, without an obvious cause, is highly suggestive of May-Thurner syndrome, and this possibility should be assessed with CT and iliac venography. It is not an infrequent source of venous abnormalities in the left lower extremity. The true prevalence of this disorder is unknown. With the move away from venography and the increased use of noninvasive diagnostic measures to confirm the presence of venous thrombosis, many cases of the left iliofemoral venous thrombosis associated with May-Thurner syndrome are probably not recognized.

The overlying artery appears to induce a partial obstruction of the vein in two ways: by its anatomic orientation with subsequent physical entrapment of the left common iliac vein and by extensive intimal hypertrophy of the vein resulting from the chronic pulsatile force of the right common iliac artery. This condition has been estimated to occur in 2%–5% of patients who undergo evaluation for lower extremity venous disorders, and it is not known why the normal anatomic relationship between the left common iliac vein and right common iliac artery is disrupted and begins to interfere with venous flow.

Reported findings show that lower extremity DVT occurs three to eight times more frequently in the left side than on the right.9) In 1943, Ehrich and Krumbhaar performed anatomic dissections in 412 cadavers and found obstructive lesions in 23.8% of the left common iliac veins. Histologically, these lesions did not represent chronic recanalized clot; rather, they were composed of elastin and collagen, without inflammatory cellular infiltration or irregular arrangement of scar. They also found that 33.8% of lesions occurred after the 1st decade of life and concluded that the lesions were acquired and not congenital.

Patients with May-Thurner syndrome typically present with unilateral (left) lower extremity edema and pain. A propensity for this disorder is seen in young women in their second to fourth decade of life, after prolonged immobilization or pregnancy. Because of the chronic nature of the disease process, patients may also present with stigmata associated with post-thrombotic syndrome such as pigmentation changes, varicose veins, chronic leg pain, phlebitis and recurrent skin ulcers. The clinical stages of iliac vein compression were described by Kim et al.,10) and include Stage I, asymptomatic iliac vein compression; Stage II, development of a venous spur; Stage III, development of left iliac vein DVT.

Although the diagnosis of May-Thurner syndrome is based on the clinical presentation of left lower extremity swelling and pain in association with radiologic evidence of compression, however, the diagnosis of May-Thurner syndrome may not always be straight forward. May and Thurner,1) have advocated the use of pressure differentials to support the diagnosis of hemodynamically significant obstruction. They have suggested1) that a pressure differential between the two iliac veins of 2 mmHg at rest or 3 mmHg with exercise is significant and that an exaggerated pressure response to exercise is a marker of significant obstruction.[1] Other authors have utilized inferior vena caval pressure as a surrogate for contralateral iliac vein pressures with the assumption that there should be little or no gradient between the inferior vena cava and the iliac vein unless obstruction is present.[11]

The finding that many patients with iliofemoral compression remain asymptomatic raises the question of whether this represents a normal anatomic variant. On the other hand, some patients with this vascular abnormality develop significant symptoms of chronic venous outflow obstruction, including pain, unilateral left lower extremity edema, venous claudication, varicose vein formation, venous stasis ulceration, and unprovoked DVT. Although, the true incidence of thrombosis in the setting of iliac compression syndrome is uncertain, there is evidence that patients in whom thrombosis develops may be at higher risk for recurrent DVT, so treatment should be started as soon as possible. Mickley et al.[12] have reported on a series of selected patients who underwent thrombectomy for iliofemoral thrombosis. Of patients with left-sided thrombosis, 49% had venous spurs found interoperatively. Prior to 1994, those spurs were untreated, and 72% of those patients had recurrent occlusive thrombosis despite treatment of at least 1 year with vitamin K antagonists. In comparison, recurrence occurred in only 1 of 28 similarly treated patients (4%) with either right-sided thrombosis or left-sided thrombosis without spur formation.

In patients in whom suspicious signs or symptoms develop, the diagnosis of May-Thurner syndrome is best made radiographically. Other causes of these symptoms, including trauma, postsurgical changes, pelvic masses, and radiation, must be excluded. Doppler ultrasound will detect the lesion if a DVT is present in the iliac vessels, but is unable to visualize iliac vein compression and spurs.[13] Other diagnostic modalities include helical abdominal CT, CT venography, magnetic resonance venography, intravenous ultrasound, and conventional venography. Kibbe et al.[14] used abdominal helical CT scanning to determine the incidence of left common iliac vein compression in an asymptomatic population. They found that two-thirds of all patients who were studied had at least 25% compression of the left iliac vein. The authors concluded that compression of the left iliac vein may be a normal anatomic finding and that abdominal CT scanning is accurate in determining if left iliac vein compression is present. There are, however, limitations for the use of abdominal CT scanning in determining if iliac vein compression is present. The CT scans were obtained during the arterial phase of the intravenous bolus, which limits the type of vessel reconstruction and analysis that can be performed. CT venography may be used as an effective adjunctive modality when there is a known DVT. Chung et al.[15] found that CT venography was just as specific and highly sensitive in the diagnosis of DVT compared with ultrasound and accurately delineated venous anatomy and the extent of thrombus present. A limitation of CT venography involves the inability to control for the volume status of the patient, which could lead to overemphasis of the degree of compression of the left iliac vein in a dehydrated patient. The traditional "gold standard" for diagnosis of May-Thurner syndrome is conventional venography, which can be diagnostic and therapeutic when endovascular therapy is used. Non-invasive imaging methods are being used increasingly to diagnose DVT and iliac compression. The aforementioned imaging modalities may help in planning catheter-directed thrombosis without the initial need for conventional venography. These non-invasive imaging modalities are simple, efficient and cost-effective in diagnosing DVT associated with iliac compression.[3]

May-Thurner syndrome is a progressive disease with substantial long-term disabling complications. An aggressive approach designed to relieve the mechanical compression should be strongly considered. Multiple surgical treatment options have been advocated. These include vein-patch angioplasty with excision of intra luminal bands, division of the right common iliac artery and relocation behind the left common iliac vein or IVC, and contra lateral saphenous vein graft bypass to the ipsilateral common femoral vein with the creation of a temporary arteriovenous fistula (Palma cross over). Overall, the reported long-term success, defined primarily as patency of the left common iliac vein or venous bypass, is 40%–88%. More recently, treatment with endovascular techniques has been described. The first known report of treatment of May-Thurner syndrome solely by endovascular means was by Berger et al. in 1995,[16] who successfully placed a venous stent to relieve iliac compression. Several subsequent studies have demonstrated efficacy in the treatment of iliac vein compression with thrombectomy and endovascular stenting. Self-expandable stents are used in the venous system as they can cover long distances, are easy to re-sheath and have adequate durability. Balloon-expandable stents may be used if needed (insufficient response to pre dilatation/self-expandable stent). Extending the stent into the IVC may be done without increasing the risk of contra lateral iliac vein occlusion.[17]

In summary, it is important to recognize that persistent edema of the left leg may be caused by May-Thurner syndrome, especially in young women. This diagnosis is confirmed with ascending iliac venography, which demonstrates the iliac vein compression. The mechanical compression should be relieved prior to the onset of DVT and venous insufficiency. Management of May-Thurner syndrome has evolved over the past few decades favoring endovascular management as the primary treatment. With early recognition and aggressive management, May-Thurner syndrome can be a well-managed disease.

## Disclosure Statement

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**Case Report**

# Huge Hemangioma in the Chest Mimicking a Breast Tumor: Report of a Case

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**A 35 year-old man first noticed an elastic mass like breast tumor in his left chest 17 years ago. It enlarged to the size of a child's head. Computed tomography showed a well-circumscribed mass in the left chest. Lumpectomy was performed. The mass was located under the thin major pectoralis muscle, covered with a white fibrous capsule. The specimen weighed 1360 g and measured 18 × 14 × 8 cm. Histological examination revealed a cavernous hemangioma. To the best of our knowledge, this is the first reported case of a chest hemangioma arising from connective tissue and located under the major pectoralis muscle.**

***Keywords:*** cavernous hemangioma, huge hemangioma, chest

## INTRODUCTION

Cavernous hemangiomas of the chest are rarely described. They do not usually grow except to keep pace with normal body growth. We report a case of a huge, cavernous hemangioma in the chest, arising from connective tissue beneath the major pectoralis muscle, that had enlarged over seventeen years.

## CASE

A 35 year-old man suffered from a huge left chest mass like breast tumor. He noticed it seventeen years ago, and it had enlarged gradually to the size of a child's head. He did not complain of pain or dysfunction of the upper limb. He consulted a university hospital and underwent a sample biopsy, which revealed a cavernous hemangioma. He was referred to our hospital for surgical resection. He had no history of trauma or injury.

On physical examination, the mass had a smooth surface and was elastic and soft, the size of a child's head located in the left chest. Striae cutis were seen in the overlying skin (**Fig. 1**). The tumor was movable and was not fixed to the chest. Computed tomography (CT) showed a huge tumor in the left chest measuring of 17 cm in diameter. The surface was smooth and well-circumscribed. The major pectoralis muscle was expanded over the tumor. Microcalcification, suggesting a phlebolith, was seen in the mass. Feeding arteries were not identified. The mass was little enhanced at the early phase and weakly enhanced at the late phase (**Fig. 2**). Gadolinium-enhancement magnetic resonance imaging (MRI) showed heterogeneous and weak enhancement.

Resection surgery was performed under general anesthesia. An oblique, spindle-shape skin incision was applied on the left chest. The mass was located under the expanded thin major pectoralis muscle and was covered with a white fibrous capsule (**Fig. 3**). The surrounding connective tissue was crude, and the tumor was easily resected by sharp and blunt dissection. The feeding arteries were small branches of the lateral thoracic artery. The excised specimen weighed 1360g and measured 18 × 14 × 8 cm. The cut surface of the specimen was dark-brown and solid. Histological examination revealed a cavernous hemangioma (**Fig. 4**). The postoperative course was uneventful, and there was no disturbance of the left upper limb. He was discharged on post-operative day 7 in good condition.

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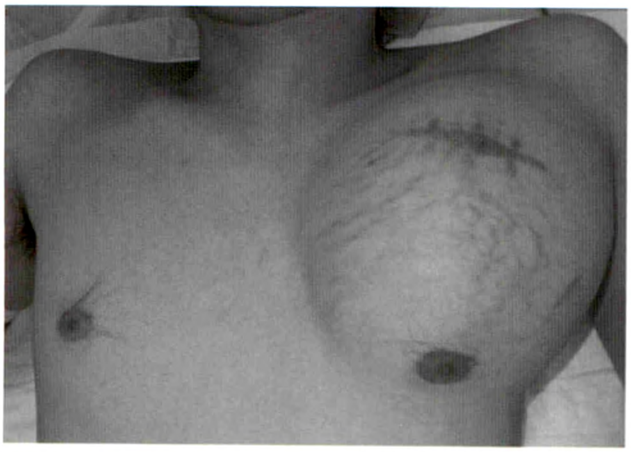

**Fig. 1** Macroscopic view of the mass: The left chest tumor was enlarged to the size of a child head. Striae cutis were seen in the overlying skin. The scar was due to the previous incisional biopsy.

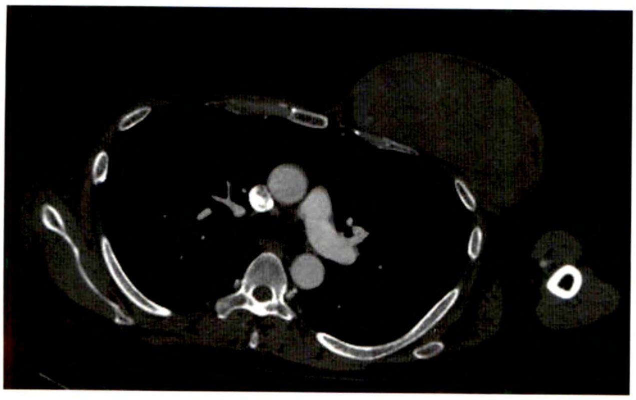

**Fig. 2** Computed tomographic scan of the chest: A huge mass of the anterior chest was slightly enhanced.

## Discussion

Cavernous hemangiomas of the chest are uncommon, benign tumors, and especially, noncutaneous cavernous hemangiomas are rare.[1,2] Differential diagnosis of the chest wall includes lipoma, schwannoma, neurofibroma, which are relatively common.

Cavernous hemangiomas typically appear at birth or before the age of 30 years, but do not usually grow except to keep pace with normal body growth.[3] In this case, the tumor had grown to the size of a child's head over a seventeen-year period.

Cavernous hemangiomas generally show distinct enhancement in contrast CT and MRI1, however, some hemangiomas do not.[4] According to a search of PubMed, three cases of chest cavernous hemangiomas as large as 10 cm or larger in diameter have been reported. In one case, contrast CT showed weak and heterogeneous enhancement.[3] In another case, contrast MRI showed slow and continuous enhancement in the peripheral portion.[5] In another case, an angiogram could identify feeder vessels.[6] In our case, contrast CT and MRI showed weak and heterogeneous enhancement, but feeding vessels could not be identified (**Table 1**).

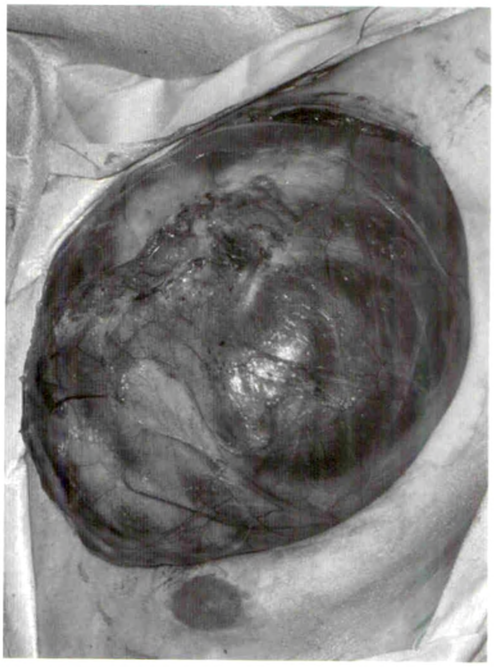

**Fig. 3** Intraoperative view of the lesion: The mass was well-circumscribed and the capsule was translucent.

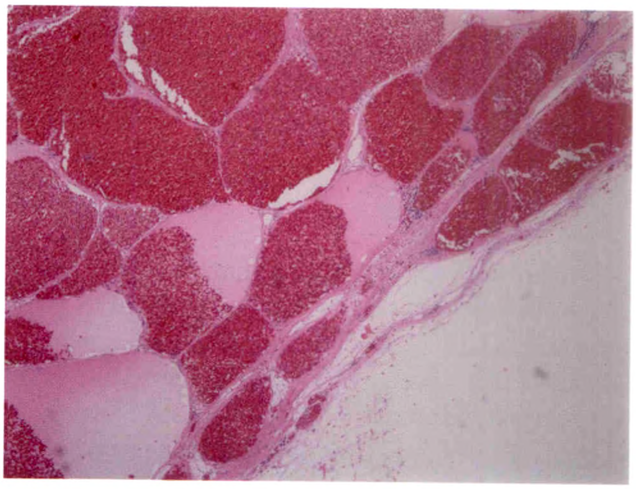

**Fig. 4** Hematoxylin and eosin-stained section: The tumor consisted of a large number of dilated vessels filled with red blood cells. (original magnification × 40)

**Table 1 Reported cases of huge cavernous hemangiomas of the chest**

| Author | Year | Age, sex | Location | Involvement of adjacent structure | Size (cm) | Weight (g) |
|---|---|---|---|---|---|---|
| Gopal | 2005 | 26 y.o., female | Breast | Skin | 12 × 10 | |
| Kim | 2006 | 18 y.o., female | Breast | Non | 13.5 × 12 × 6 | 660 |
| Kinoshita | 2005 | 60 y.o., male | Breast | Rib | 14 | 2050 |
| Our case | 2011 | 35 y.o., male | Chest wall (under major pectoralis muscle) | Non | 18 × 14 × 8 | 1360 |

y. o.: year-old

Although chest cavernous hemangiomas in the mammary gland[5] and subcutaneous tissue[7,8] have been reported, there was no reported case of hemangioma arising from connective tissue under the major pectoralis muscle. This case is the first reported case. In the three reported cases of huge chest cavernous hemangiomas, a skin change simulating an inflammatory carcinoma appeared in one case.[6] In the other three cases, including our case, there was no change of the overlying skin. Three cases including ours had no involvement of the ribs or deeper structure, but one case involved ribs and intercostal muscle and radical resection was performed (**Table 1**).[3]

Although chest cavernous hemangiomas are benign, complete resection is recommended to exclude the possibility of underlying angiosarcoma.[3]

## CONCLUSIONS

Huge chest cavernous hemangiomas may not show a distinct enhancement in contrast CT or MRI differently from other typical cavernous hemangiomas. Although chest cavernous hemangiomas in the mammary gland and subcutaneous tissue have been reported, our case is the first reported case of cavernous hemangioma arising from connective tissue under the major pectoralis muscle.

## DISCLOSURE STATEMENT

Masao Tadakoshi and coauthors have no conflict of interest.

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**Case Report**

# Staged Hybrid Debranching and Thoracic Endovascular Aneurysm Repair for Multiple Aortic Aneurysms after Conventional Open Repair of the Descending Aorta: A Case Report

Yukihiro Matsuno, MD, PhD, Katsuya Shimabukuro, MD, PhD, Narihiro Ishida, MD, PhD,
Yukiomi Fukumoto, MD, PhD, and Hirofumi Takemura, MD, PhD

**Endovascular repairs of thoracic and thoracoabdominal aortic aneurysm have recently been proposed as a less invasive alternative to conventional open surgical repair. In selective cases, adjunctive bypass surgery may be required to provide an adequate landing zone. We describe a case of staged hybrid debranching and thoracic endovascular aneurysm repair for distal aortic arch and thoracoabdominal aortic aneurysms after conventional open repair of the descending aorta.**

***Keywords:*** thoracic endovascular aneurysm repair, debranching, multiple aortic aneurysm

## INTRODUCTION

Since the first successful endovascular thoracic aortic aneurysm repair, performed by Dake and colleagues in 1994,[1] endovascular repair has evolved into a valuable treatment for thoracic and aortic aneurysm. This technique is less invasive with low morbidity and mortality for high-risk patients, especially those who have undergone prior open aortic surgery.[2] In cases of aortic arch or thoracoabdominal pathologies, which often involve the origin of the supra-aortic or visceral-renal branches, it may be necessary to cover those branches using an endovascular stent graft to extend the proximal or distal landing zone. To reduce the risk of neurologic and vascular complications, adjunctive open surgical bypass surgery may be required to provide an adequate landing zone.[3] This is a case report of staged hybrid debranching and thoracic endovascular aneurysm repair for multiple aortic aneurysms after conventional open surgical repair of the descending aorta.

## CASE REPORT

A 71 year-old man was referred to our hospital with the diagnosis of multiple aneurysms in the distal aortic arch and thoracoabdominal aorta. He had undergone conventional open repair of the proximal descending aorta through a left lateral thoracotomy eight years ago. A computed tomography (CT) scan showed a distal aortic arch aneurysm just below the left subclavian artery (LSCA) with a maximum diameter of 51 mm and a thoracoabdominal aortic aneurysm just below the previous distal anastomotic level of the prosthetic graft, involving the celiac artery (CA) and the superior mesenteric artery (SMA) with a maximum diameter of 61 mm (**Fig. 1**). Because the patient was insistent in avoiding a redo thoracotomy and declined a conventional, open surgical treatment and strongly requested a less invasive treatment, we chose the thoracic endovascular aneurysm repair (TEVAR). As those aneurysms were closed to the left common carotid artery (LCCA) and involved the CA, adjunctive surgical bypass grafting was needed to provide adequate landing

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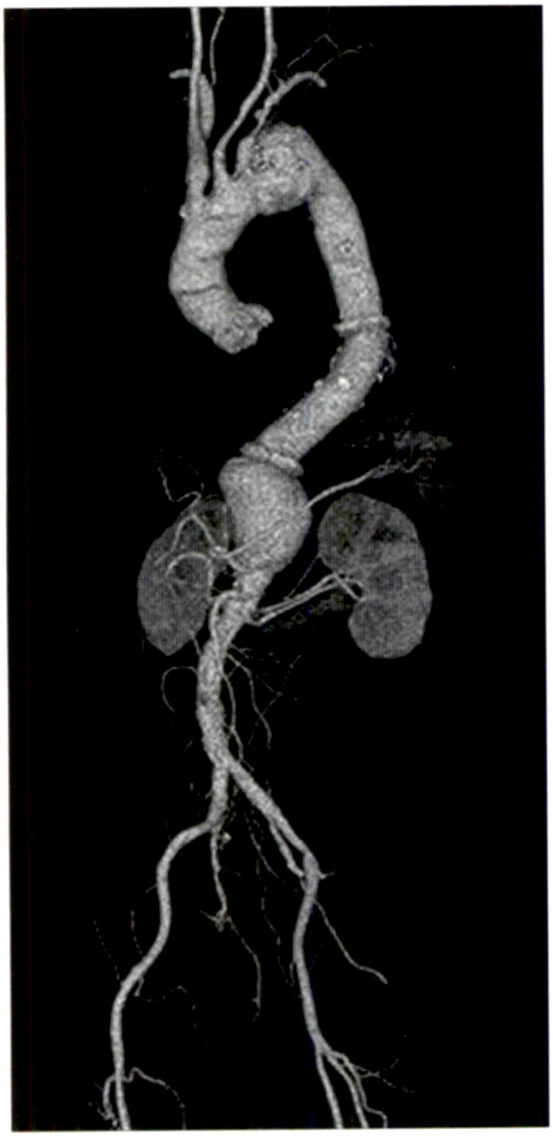

**Fig. 1** Preoperative 3-dimensional computed tomography (3D-CT) showed multiple aneurysms in the distal aortic arch and thoracoabdominal aorta.

zones for TEVAR. As a result, we decided to perform staged hybrid debranching and TEVAR.

Under general anesthesia, bilateral axillary arteries were exposed through an infraclavicular incision parallel to the clavicle and the left common carotid artery was exposed through a longitudinal incision along the medial aspect of the left sternocleidomastoid. An extra-anatomic right-to-left axillary artery bypass was performed in an end-to-side fashion using a ringed Gore-Tex 8 mm graft (W.L. Gore and Associates, Inc., Flagstaff, AZ). Then the LCCA-to-the prosthetic graft bypass was performed using another Gore-Tex 8 mm graft and the root of the LCCA was ligated to prevent retrograde perfusion into the aneurysm. There was no change of regional cerebral oxygen saturation during carotid artery clamping according to cerebral oxymetry monitoring. Following those procedures, a 37 mm × 20 cm Gore TAG thoracic endoprosthesis (W.L. Gore and Associates, Inc., Flagstaff, AZ) was deployed from just distal to the origin of the innominate artery to the proximal part of the previous prosthetic graft through a right common iliac artery. A completion angiogram demonstrated no evidence of retrograde type II endoleak. Therefore, proximal ligation or coil embolization of the LSCA was not performed. There were neither neurologic nor vascular complications. Postoperative CT scan revealed complete exclusion of the aneurysm without any evidence of leakage and good patency of the bypass grafts (**Fig. 2**). He was discharged on postoperative day 11th.

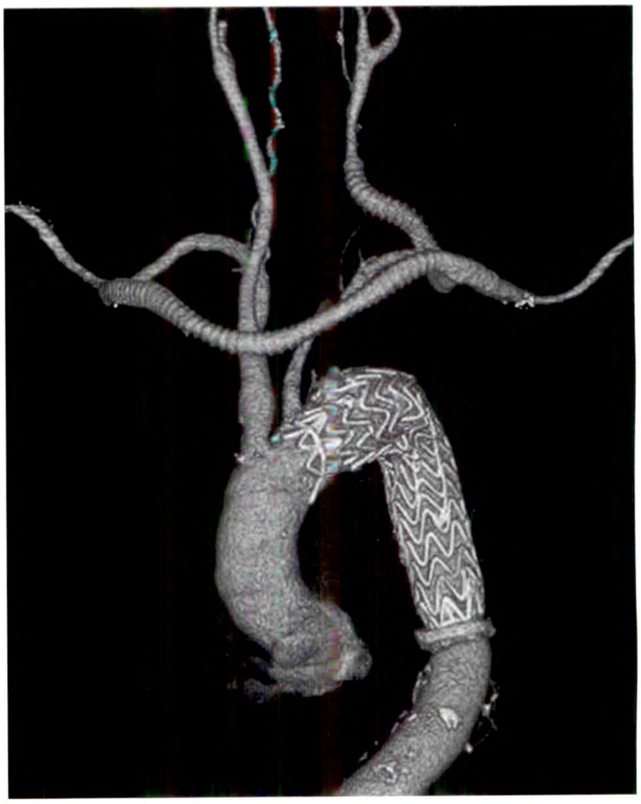

**Fig. 2** 3D-CT after the fist hybrid debranching and thoracic endovascular aneurysm repair for distal aortic arch aneurysm.

The patient was readmitted to our hospital for surgical treatment of the thoracoabdominal aortic aneurysm 3 months after the first operation. Prior to the second operation, the celiac artery balloon occlusion test was performed, and intact collateral foregut circulation between the celiac and superior mesenteric arteries was confirmed. Operation was performed thorough a median

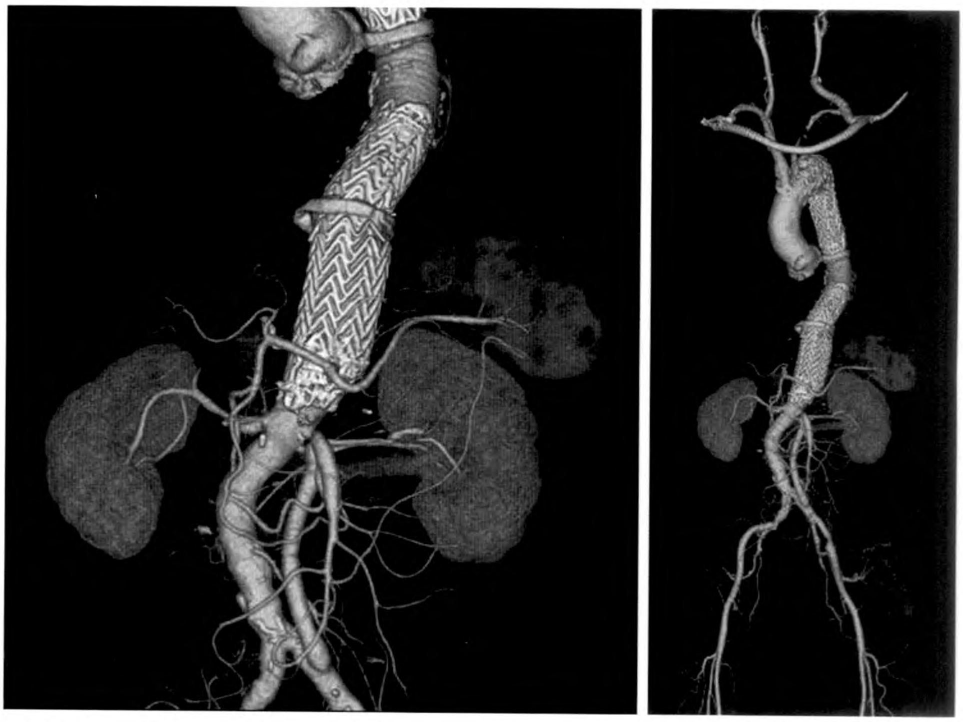

**Fig. 3** 3D-CT after the second hybrid debranching and thoracic endovascular aneurysm repair for thoracoabdominal aortic aneurysm.

laparotomy under general anesthesia. Spinal cord protective measures, including cerebral spinal fluid drainage, motor-evoked potential, and prevention of intraoperative and perioperative hypotension were used during this staged procedure. The CA, the SMA and the left common iliac artery (LCIA) were exposed in preparation for the bypass grafting. The LCIA was used as the donor vessel of inflow for the retrograde SMA bypass graft. The SMA was anastomosed end-to-side fashion using a ringed Knitted Dacron 8 mm graft (Gelsoft®, Vascutek). Following those procedures, a 31 mm × 15 cm Gore TAG thoracic endoprosthesis was deployed from the distal part of the previous prosthetic graft to just above the bilateral renal arteries through a terminal abdominal aorta. Then, the root of the CA and SMA was ligated to prevent retrograde perfusion into the aneurysm. Postoperative CT scan showed complete exclusion of the aneurysm without any evidence of leakage and good patency of the bypass grafts (**Fig. 3**). His postoperative course was uneventful without any complications, and he was discharged 20 days after the surgery.

## DISCUSSION

The long-term results of most thoracic or thoracoabdominal aortic aneurysm repairs are satisfactory. However, some patients require a reoperation for a separate aneurysm after the original aortic repair. Thus, in cases of thoracic or abdominal aortic aneurysms there is quite a high risk of development of multiple aortic aneurysms. Carrel et al. reported that new or recurrent aortic aneurysms accounted for 36 (27.7%) of the 130 thoracic aortic reoperations performed in their series of 120 patients were due to new or recurrent aortic aneurysms.[4] Crawford's complete TAAA experience reported by Svensson and colleagues, 181 patients (12%) had previously undergone a proximal aortic operation; this group of patients was characterized by a lower 30-day mortality rate than in the group of patients who had not previously undergone thoracic aortic aneurysm repair.[5]

Endovascular repair of thoracic pathology is emerging as the preferred treatment strategy in a majority of patients, as increasing data suggest that endovascular repair may be performed with lower perioperative morbidity and mortality rates, with similar midterm survival, when compared with conventional open surgical repair.[6] However, because of anatomic constraints related to required endograft seal zones, a significant number of patients, many of whom are not ideal candidates for open surgery, are excluded from standard endovascular repair. Consequently, in an attempt to expand the pool of patients suitable for endovascular repair, "hybrid" techniques, including open aortic arch and thoracoabdominal debranching procedures, have been described to allow creation of proximal and/or distal landing zones for stent graft seal.[3] Current data suggest that these techniques of hybrid debranching and TEVAR (H-TEVAR) could be performed with lower rates of morbidity and mortality than could conventional, open surgical repair.[7,8]

By avoiding thoracotomy, H-TEVAR may be hypothesized to be particularly advantageous in the case of previous descending thoracic aortic repair in which a redo left-sided thoracotomy may be associated with major bleeding, increased rate of postoperative respiratory and organ failure, longer distal aortic perfusion time, longer total aortic clamping time, longer operation time, and reduced long-term survival.[2,9] It is interesting to hypothesize that existing thoracic or abdominal tube grafts in H-TEVAR may offer optimal in-graft landing zones for endografts and ideal inflow sites for visceral bypasses.

When the distal landing zone proximal to celiac artery is inadequate, either a thoracoabdominal approach or debranching of visceral vessels is required, followed by TEVAR. Another alternative includes extending the distal landing zone by covering the celiac artery origin. In our present case, the celiac artery balloon occlusion test was performed, and intact collateral foregut circulation was confirmed. Preoperative angiography is recommended to assess the collateral circulation between the celiac and superior mesenteric arteries before coverage of the celiac artery.[10]

The staged operation has several advantages, one of which was less invasive for the patient, including shorter operation times and potentially decreases the risk of renal failure from contrast load during the operation. Moreover, it is likely that the staged procedure contributes to the preservation of spinal cord perfusion through collateral arterial flow, which may result in lower paraplegia rates.

In conclusion, hybrid debranching and TEVAR expand the available surgical options for patients with multiple thoracic aortic aneurysms, and they appear to be a safe alternative to open repair for thoracoabdominal and aortic arch aneurysms in properly selected patients with significant comorbidity or prior open aortic surgery.

## DISCLOSURE STATEMENT

The authors declare that they have no competing interests.

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**Case Report**

# A Case of Embolism due to a Floating Thrombus Migrating from the Left Atrial Appendage to the Ostium of the Celiac Artery

Takashi Ando, MD, PhD, Hiroyuki Abe, MD, PhD, and Daijun Ro, MD

**The present case was a 70 year-old dialysis patient who had experienced a prior cerebral infarction following atrial fibrillation. Her shunt suddenly occluded during dialysis, and she was transferred to our hospital. Transesophageal echocardiography revealed a floating, ball-like thrombus in the left atrial appendage (LAA). After thrombectomy in the shunt, acute thrombi were extracted. Despite anticoagulant therapy, the ball-like thrombus in the LAA did not dissipate and instead continued to enlarge. We planned surgical intervention involving a left atrial appendectomy without cardiopulmonary bypass through a left thoracotomy. However, her thrombus disappeared out of the LAA when she was intubated in the operating room. Her surgery was, therefore, stopped, and extubation was carried out. A computed tomography (CT) scan showed that the embolism had moved to the ostium of the celiac artery. Incidentally, this celiac artery had already been obstructed, and her inferior mesenteric artery had been the main supply of blood flow to the intestine, explaining why she had not developed intestinal ischemia. We continued anticoagulant therapy with warfarin. Follow-up CT studies were conducted at the outpatient clinic. However, the patient died due to a wide cerebral infarction before the 6-month checkup.**

*Keywords:* floating thrombus, atrial fibrillation (AF), left atrial appendage (LAA), nonvalvular atrial fibrillation (NVAF)

## INTRODUCTION

Cerebral infarction in patients with atrial fibrillation (AF) may vary from clinically silent to catastrophic. The incidence of AF increases with age. Not only AF with valvular heart diseases, but also nonvalvular atrial fibrillation (NVAF), represents causes of embolic stroke. In addition, the left atrial appendage (LAA) is a common source of cardiac thrombus formation and systemic embolism. It is a 'blind' rod-shaped pouch that may promote hemostasis.[1] However, there is little information available about the incidence of thrombus in the LAA with NVAF in noncerebral acute arterial occulsion.[2] We herein report a case of embolism due to a floating thrombus that migrated from the LAA to the ostium of the celiac artery in a dialysis patient with NVAF.

## CASE REPORT

A 70 year-old female was transported to an emergency hospital with a complaint of pain in the left upper arm on the side of the shunt at the time of dialysis. The shunt sounds had already disappeared. The patient's history revealed that she had been taking warfarin since she had cerebral infarction with AF at 50 years of age. On admission to our hospital, her temperature was 36.0°C, her blood pressure was 120-/65Torr, and her heart rate

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*This summary was presented at the Poster Session of the 52nd Annual Meeting of Japanese College of Angiology, Gihu, Japan, October 2011.

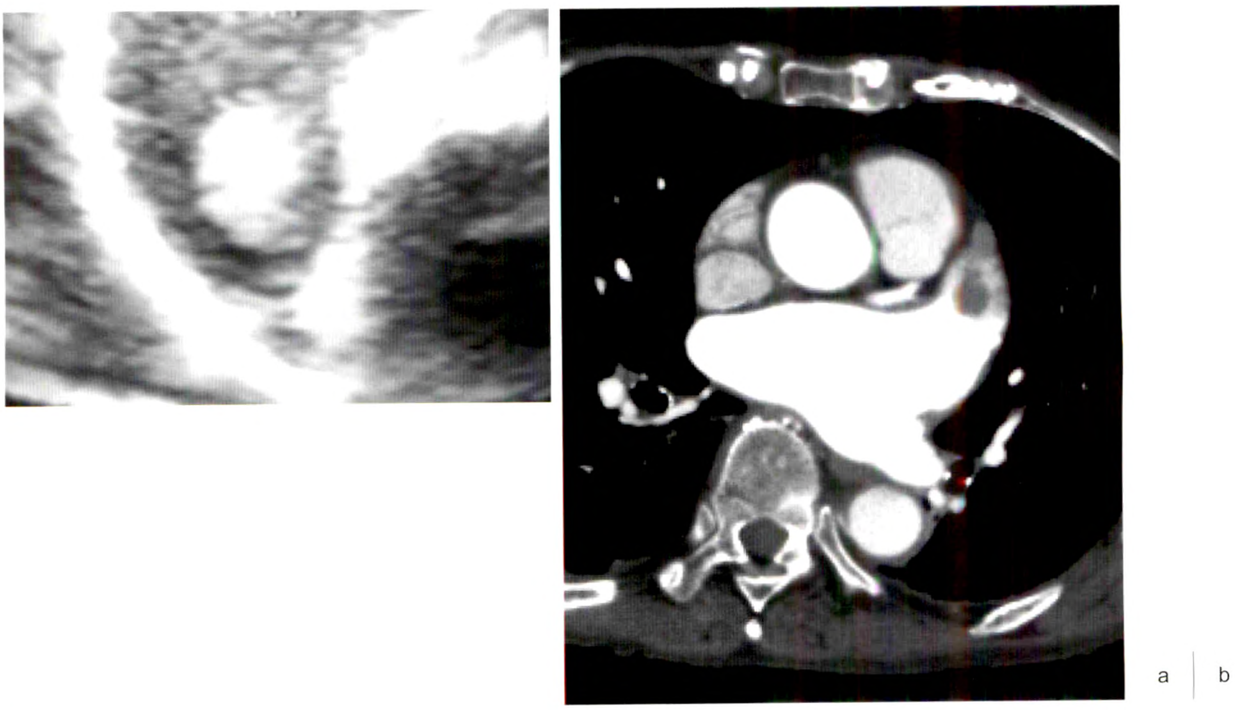

**Fig. 1** Transesophageal cardiac sonography showed the ball-like floating thrombus in the LAA. (**a**) Enhanced CT revealed that a thrombus in the LAA (**b**).
LAA: left atrial appendage

was 90/min irregular rhythm. The hematological data indicated both anemia and compromised renal function that were as follows: Hb 9.2 g/dl, BUN 55.3 mg/dl, Crea 8.91 mg/dl. The results of biochemical tests of liver function and inflammatory reactions were within normal limits. However, taking warfarin was insufficient anticoagulation therapy since her PT-INR was 1.00. The chest and abdominal X-rays showed no abnormal findings. Ultrasonic arteriography on the shunt side showed the presence of an embolism in the bifurcation of the left brachial artery. Transthoracic ultrasonic cardiography revealed that her cardiac function was good without valvular dysfunction. Her AF was NVAF, but no thrombus in the cardiac chamber was noted. We then performed transesophageal echocardiography to detect the origin of the embolism,[3] which revealed a ball-like floating thrombus in the LAA. Enhanced computed tomography (CT) scan also illustrated the presence of a thrombus in the LAA and left upper artery without the involvement of other sites (**Fig. 1a** and **1b**). We speculated that the embolism from the surface of the left atrial appendage thrombus suddenly occluded her shunt.

The patient underwent an emergency thrombectomy for her left arm under local anesthesia. The arterial flow was recanalized immediately after red thrombi were extracted. Both the operative findings and histological examination of the thrombi indicated that they were fresh. Next, we planned to extract the ball-like thrombus in the LAA. We judged that using cardiopulmonary bypass would be high-risk based on her generally poor condition due to that fact that she had a more than 20 year dialysis history and disuse syndrome following an old cerebral infarction. Therefore, conservative treatment was started, and the progress of the LAA thrombus was monitored intensely. We controlled her APTT ranged 60 to 90 using heparin, because we did not use warfarin at the moment, for prevention of emergent surgical bleeding. However, the size increased slightly for three days, and the ball-like thrombus was still moving in the LAA. Because the risk associated with the embolism increased, we decided to perform excision of the LAA, including the thrombus, under a left thoracotomy without the patient on cardiopulmonary bypass.

On the fourth admission day, she was ready for the operation. Under general anesthesia, she was intubated, and an esophageal echo probe was inserted. The patient was placed in the head-down position to insert the central venous line in the right jugular vein. At that time, the

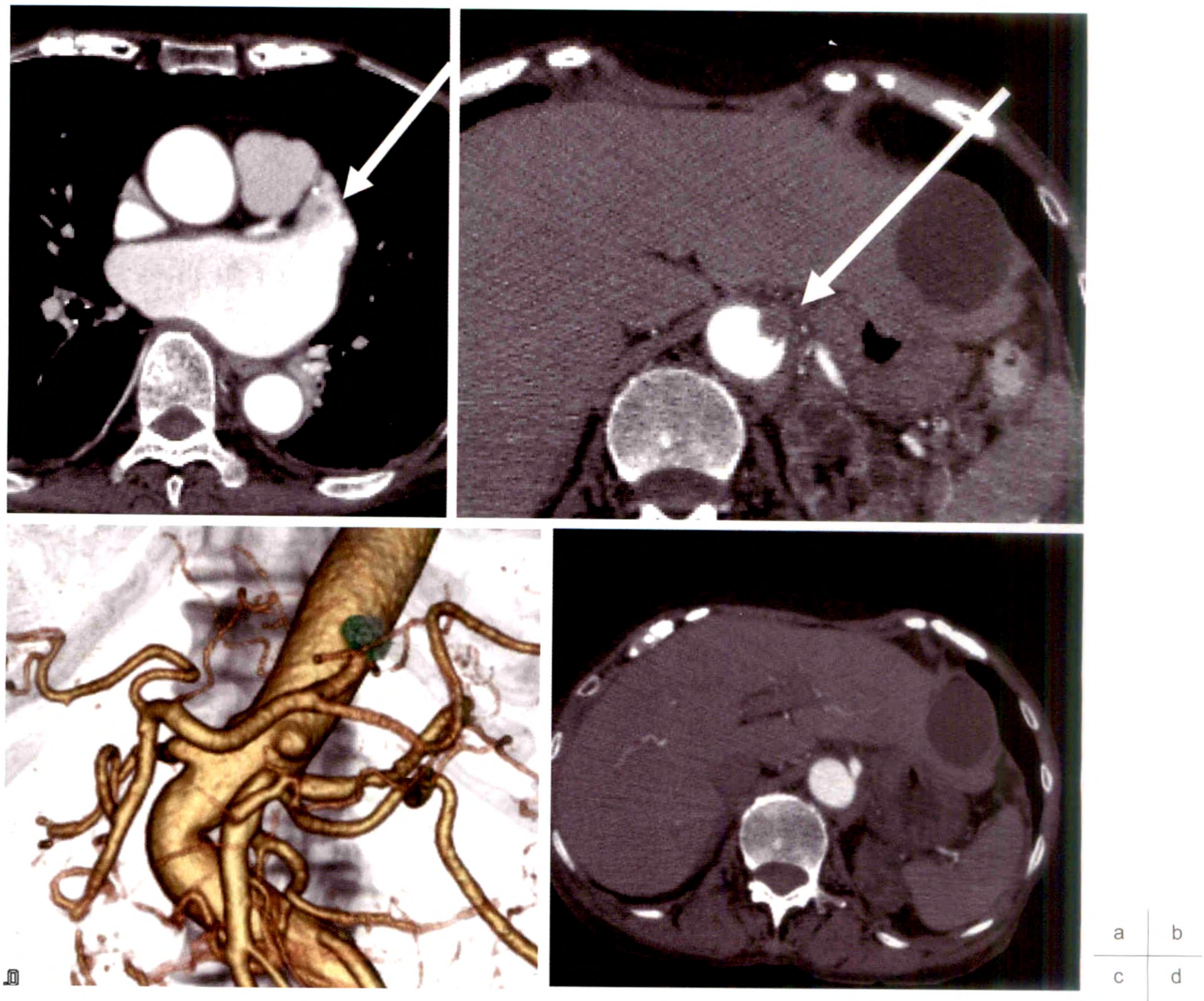

**Fig. 2** (**a**) Enhanced CT showed no thrombus in the LAA. (**b**) It also displayed the ostium of the celiac artery. (**c**) 3-D CT illustrated the position of the embolism. (**d**) showed the stenosis of the ostium of the celiac artery at the time of admission without thromboembolism.
LAA: left atrial appendage

echo probe indicated that the moving ball-like thrombus had disappeared out of the LAA. There was no thrombus image in any of the cardiac chambers. We immediately awoke the patient from anesthesia, and she was extubated in the operating room without any abnormal neurological findings. An enhanced CT scan was conducted to identify the new location of the embolism. While the ball-like thrombus had been a lump, it was identified in the ostium of the celiac artery in the abdominal aorta (**Fig. 2a–2d**). Coincidentally, the celiac blood flow was not significant, and it was supported by collateral circulation from a developed inferior mesenteric artery. In short, because the ostium of the celiac artery was already stenosed, and the superior mesenteric artery had occluded, non-intestinal tract ischemia was caused by this embolism. While surgical and catheter intervention were also taken into consideration, we continued conservative medical therapy. It was concluded that if this ball-like thrombus had been carried lower, it would have be easy to perform thrombectomy of the leg. A seventh day follow-up enhanced CT scan showed the same position of the embolism and no abnormality of the intestinal circulation. After controlling her anticoagulotherapy with warfarin ranging PT-INR from 2.0 to 3.0, the patient was discharged from the hospital without complications.

Although warfarin management was continued in the dialysis hospital, the patient died of an extensive cerebral infarction six months later.

## DISCUSSION

It has been reported that 90% of LAA thrombi in patients with NVAF are accepted in the left atrium.[1] The structure of the LAA is a rod-shaped pouch that may have stagnant blood flow, leading to hemostasis.[1] Abe et al.[4,5] reported that LAA thrombi could be classified into three types: the mobile ball type, fixed ball type, and mountain ball type. The mobile ball type is associated with an especially high risk of embolism. The present case had a ball-like floating embolism, which belongs to the mobile ball type. However, why the thrombus lodged on the orifice of the celiac artery with decreased flow, mainly supplying blood flow to the splanchnic organs came from inferior mesenteric artery? One of our speculations was that since it was the first branch that came out in the main artery before vessel bending due to arteriosclerosis, it would arise a certain turbulent flow there.

The optimal medical intervention for the treatment of such cases is still controversial. There have been various recent reports about LAA excision.[6,7] These reports insisted that both decreased atrial contraction and secretion of human natriuretic peptide might not play important roles just after left appendectomy. Various methods for performing a left atrial appendectomy were reported.[6,7] We had often closed the LAA using tobacco sutures inside of the left atrium, or double ligation outside of the LAA. However, a risk of a residual leak flow was associated with these methods, and was considered to thrombosis in those reports.[8–10] Therefore, the surgical technique, as well as the catheter device, should be carefully considered when developing a standard treatment for left appendectomy with AF. At present, the existing data suggest that left atrial appendectomy is a suitable operation for preventing LAA thrombus and decreasing the risk of cerebral infarction.

The death of this patient seemed to be caused by the thrombus recurred at the LAA due to poor control of the coagulation system. Consequently we highly illustrated that floating thrombus in the LAA should be considered for emergent operation firstly instead of the very strictly limited cases.

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**Case Report**

# Femoral Vein Compression Resulting from a Ganglion of the Hip Joint: A Case Report

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**The development of a ganglion in the hip joint is a rare cause of lower limb swelling. We herein describe a case of a ganglion of the hip with compression of the femoral vein that produced signs and symptoms that mimicked a deep vein thrombosis. Needle aspiration of the ganglion was easily performed, and swelling of the left lower limb promptly improved. Intensive follow-up of this case was important because the recurrence rate of ganglions after needle aspiration is high.**

***Keywords:*** ganglion, deep vein thrombosis, pseudothrombophlebitis

## INTRODUCTION

Synovial/ganglion cysts of the hip joint are rare. Compression of the femoral vein by a synovial/ganglion cyst of the hip joint result in leg swelling resembling that caused by deep vein thrombosis.1) We herein present a case of lower limb swelling due to compression of the femoral vein by a ganglion of the hip joint.

## CASE REPORT

An 85 year-old female came to our hospital with a three-month history of swelling and edema of the left leg. The left thigh circumference was measured to be 4 cm greater, and the left calf circumference was measured to be 2 cm greater than that of the right leg. The grayish-purple color of the left lower limb suggested venous stasis; however, the patient did not complain of either pain or tenderness in the left leg (**Fig. 1**). Ultrasonography (U.S.) was performed. No venous thrombi were seen; however, U.S. showed a cystic lesion posterior to the left femoral vein, measuring approximately 3 cm in diameter. The left femoral vein curved anteriorly and was severely compressed by the lesion. A computer tomography (CT) scan and magnetic resonance imaging (MRI) of the left hip region revealed, both in high-T2- and low-T1-weighted signal intensity, a cystic lesion 3 cm in diameter arising from the anterio-medial aspect of the acetabulum (**Fig. 2**). Needle aspiration of the cyst was easily performed with a 21-gauge short needle under U.S. guidance. Approximately 2 mL of clear, jelly-like fluid was yielded (**Fig. 3**). The size of the cyst had decreased, and the swelling of the left lower limb promptly improved; therefore, the patient did not require surgery for the ganglion cyst of the hip joint. No recurrence of swelling of the left lower limb was observed up to two months after the needle aspiration.

## DISCUSSION

The development of cystic lesions around the joints is a common clinical problem. Histologically, there are two types of cysts; ganglia and synovial cysts. Synovial cysts usually demonstrate a communication with the adjacent facet joint and have a lining of synovial cells seen on a histologic analysis. Ganglion cysts are thought to be the result of myxomatous degeneration of certain fibrous

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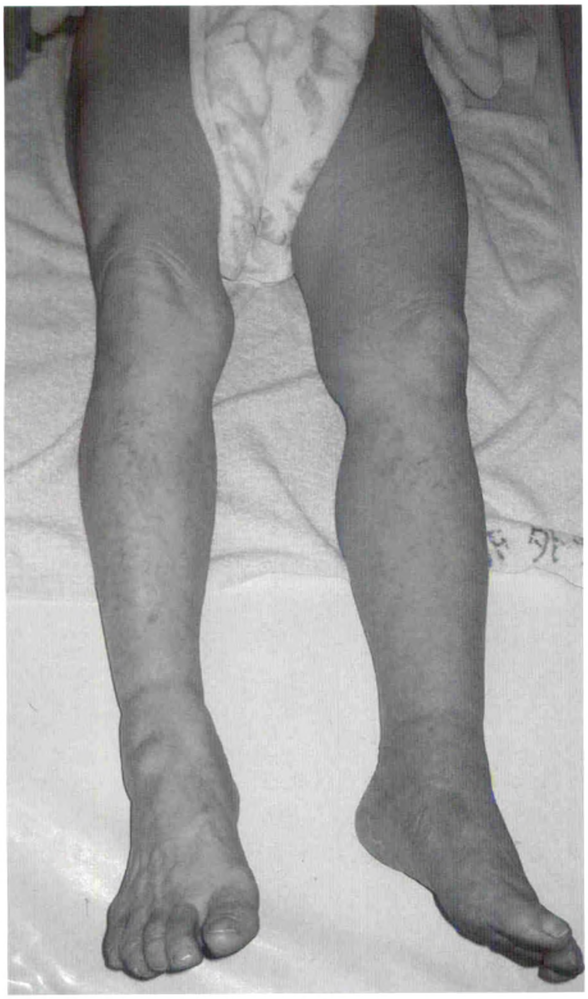

**Fig. 1** Lower limbs of the patient at the first visit.
The left lower limbs were swollen and the skin was grayish-purple, suggesting venous hemostasis.

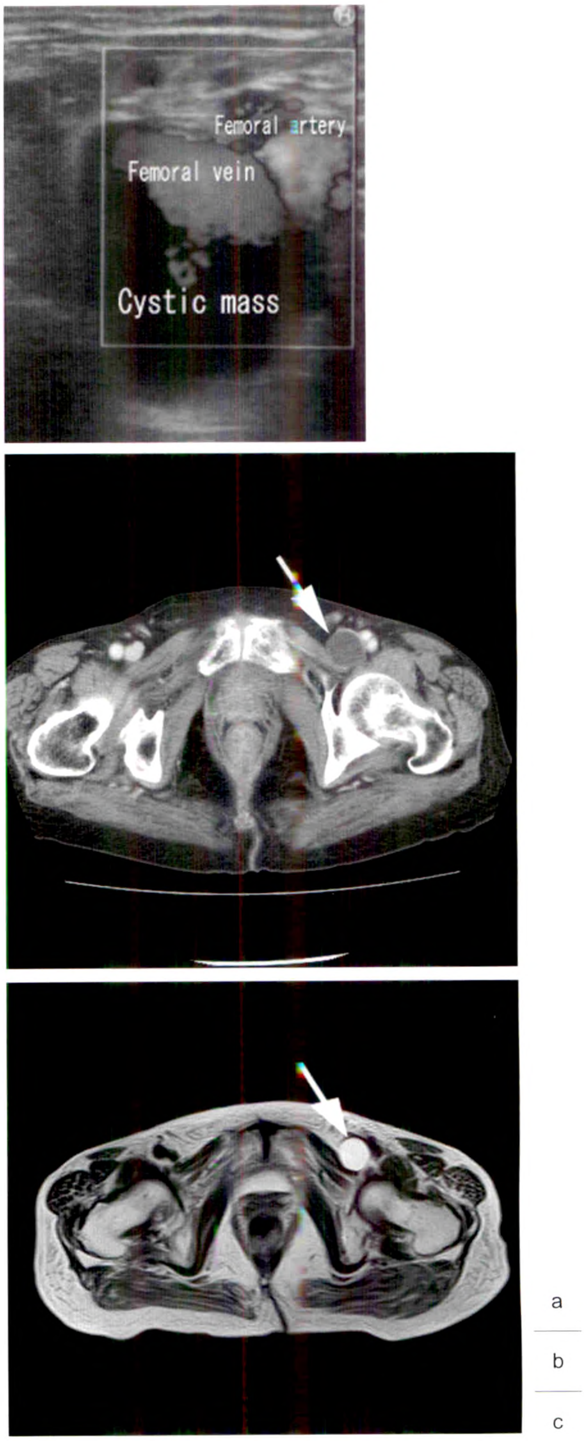

**Fig. 2** US, CT, and MRI findings.
US (**a**), CT (**b**), and MRI (**c**) each showed a cystic mass (arrow) arising from the left hip joint compressing the femoral vein.

tissue structures, and they do not have a lining of synovial cells on a histologic analysis.[2)] Because symptoms of and therapy for para-articular cysts do not depend on the histologic composition of the cyst wall, differentiation of ganglia and synovial cysts may be more of academic interest than of clinical importance. Moreover, distinguishing between ganglia and synovial cysts using imaging is not always possible, so that the terms ganglion and synovial cyst are often used interchangeably.[2)] Synovial/ganglion cysts can develop on any joint lining or tendon sheath, though, they usually occur at the wrist, ankle, or knee. Synovial/ganglion cysts of the hip joint are not common and are usually accompanied by hip disorders such as rheumatoid arthritis, osteoarthritis, or trauma. The development of an inguinal mass and the presence of groin or thigh pain form the usual clinical presentation of synovial/ganglion cysts. However, compressive symptoms caused by synovial/ganglion cysts of the hip joint are unusual. Compression of the femoral or iliac vein causes leg swelling resembling that caused by deep

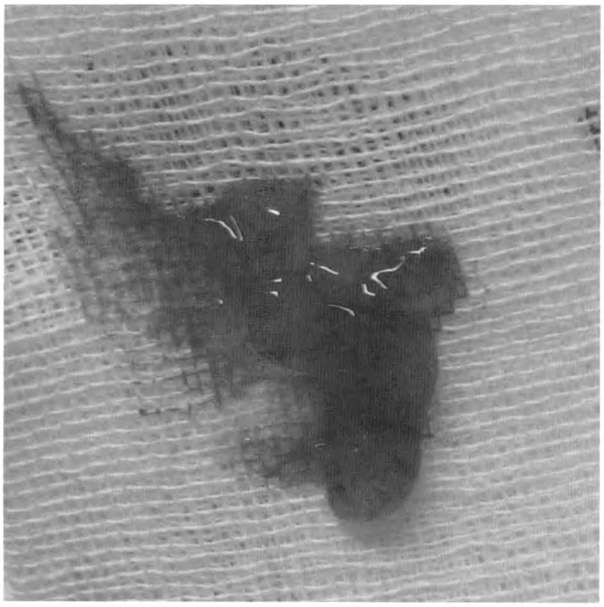

**Fig. 3** The content of the cystic mass obtained by needle aspiration. Clear, jelly-like fluid was yielded.

vein thrombosis,[1,3–5] called pseudothrombophlebitis, and sometimes induces deep vein thrombosis,[6] called pseudo-pseudothrombophlebitis. Compression of the femoral artery causes leg ischemia,[7] and compression of the femoral nerve causes femoral nerve palsy.[8]

In 2006, Colasanti et al. reported their case and summarized 27 previously reported cases of lower limb swelling caused by synovial cysts of the hip joint. The mean age of these patients was 62 (35–80) years, and 60% of the patients were female. In 55% of the cases, the joint cysts were accompanied by hip disorders: rheumatoid arthritis or osteoarthritis. Surgery was the treatment of choice in 70% of the cases, and the remaining cases were treated with needle aspiration. Lower limb swelling recurred in 37% of the patients initially treated with needle aspiration, whereas recurrence was noted in only one patient treated surgically.[5]

Radiographs are useful to observe the presence of hip disorders. Arthrography can be used to demonstrate the communication of a cyst with the joint cavity; however, cysts may fail to fill when the communication is very narrow or when the cyst is filled with highly viscous fluid. Ultrasonography is one of the most useful imaging modalities; it facilitates diagnosis and is not invasive. However, ultrasonography does not show subtle sites of joint communication and has a limited ability to evaluate associated intra-articular abnormalities. Furthermore, cysts containing debris or hyperplastic synovium may simulate solid mass lesions on an ultrasound examination. A computer tomography (CT) scan is an excellent tool to assess abnormalities of calcified tissues because of its high spatial resolution. Nonetheless, its value for assessing soft-tissue contrast is still limited. Para-articular cysts have lower attenuation than muscle and higher attenuation than fat. Rim enhancement is seen after administration of intravenous contrast. Magnetic resonance imaging (MRI) is superior to all other imaging modalities for investigating soft-tissue abnormalities, particularly for demonstrating the location and extent of lesions. It offers superior soft-tissue contrast and multiplanar capabilities and is noninvasive. It demonstrates the exact location and extent of a lesion, shows the relationship of a lesion to the joint and surrounding structures, and with the aid of intravenous contrast, shows rim enhancement that indicates the cystic nature of a lesion. In addition, MRI is very accurate in depicting associated joint disorders such as meniscal tears, ligamentous abnormalities, and degenerative or inflammatory changes.[2]

Treatment of synovial/ganglion cysts depends on their size, location and symptoms. Asymptomatic synovial/ganglion cysts are often treated with observation. Once a synovial/ganglion cyst of the hip joint causes compressive symptoms, the ideal treatment is surgical excision because the recurrence rate for cysts treated with needle aspiration is high. However, needle aspiration is easier to perform and is less invasive than surgery, and the contents of a cyst can aid diagnosis.[1]

In the present case, we treated the cystic mass with needle aspiration only; therefore, no histological diagnosis was done. The CT and MRI revealed no direct communication of the cystic mass and the hip joint, and the CT and MRI findings were similar to that found in cases of ganglia of the hip joint previously reported by Gale et al.[6] and Bhan et al.[4] Therefore, we diagnosed the cystic mass as a ganglion. Because the patient's leg swelling promptly improved, she did not request surgery. Surgery has been recommended for the treatment of synovial cysts because of frequent recurrence after needle aspiration. However, according to Savarese et al.,[9] surgical excision should be reserved for patients with recurrent cysts or for those who do not respond to needle aspiration. Ideally, surgery was indicated in this case, and a careful follow-up was needed because of the high possibility of recurrence

## CONCLUSIONS

We herein report a rare case of leg swelling due to femoral vein compression by a ganglion of the hip joint. Ganglia of the hip joint should be taken into consideration in the differential diagnosis of deep vein thrombosis. Needle aspiration is one of the more useful and less invasive options to treat ganglia; however, the recurrence rate following this procedure is high.

## DISCLOSURE STATEMENT

We declare no conflicts of interest.

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# 【ERRATUM】

The publisher would like to draw readers' attention about following article appeared as Case Report in our journal, Annals of Vascular Diseases vol.5 iss.1 p.85.

Title:
Endovascular Stenting for Left Subclavian Venous Stenosis for a Hemodialysis Patient with a Persistent Left Superior Vena Cava

Authors:
Tomohiro Matsumoto, Takuji Yamagam, Hiroyuki Morishita, Shunsuke Asai, Osamu Sato, Tsuneyuki Nakanouchi, and Tsunehiko Nishimura

The second author's name should be as follows:

Takuji Yamagami

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# 冷感、疼痛、潰瘍の改善に。

**【禁忌(次の患者には投与しないこと)】**
**(1)出血している患者(血友病、毛細血管脆弱症、上部消化管出血、尿路出血、喀血、眼底出血等)**
**(2)妊婦又は妊娠している可能性のある婦人**

**【効能・効果】**
○慢性動脈閉塞症に伴う潰瘍、疼痛及び冷感の改善
○原発性肺高血圧症

**<効能・効果に関連する使用上の注意> 原発性肺高血圧症**
(1)原発性肺高血圧症と診断された患者にのみ使用すること。
(2)本剤は経口投与であるため、重症度の高い患者等では効果が得られにくい場合がある。循環動態あるいは臨床症状の改善が見られない場合は、注射剤や他の治療に切り替えるなど適切な処置を行うこと。

**【用法・用量】**
○**慢性動脈閉塞症に伴う潰瘍、疼痛及び冷感の改善**　通常、成人には、ベラプロストナトリウムとして1日120μgを3回に分けて食後に経口投与する。
○**原発性肺高血圧症**　通常、成人には、ベラプロストナトリウムとして1日60μgを3回に分けて食後に経口投与することから開始し、症状(副作用)を十分観察しながら漸次増量する。増量する場合には、投与回数を1日3〜4回とし、最高用量を1日180μgとする。

**<用法・用量に関連する使用上の注意> 原発性肺高血圧症**
原発性肺高血圧症は薬物療法に対する忍容性が患者によって異なることが知られており、本剤の投与にあたっては、投与を少量より開始し、増量する場合は患者の状態を十分に観察しながら行うこと。

**【使用上の注意】(抜粋)**
**1.慎重投与(次の患者には慎重に投与すること)**　(1)抗凝血剤、抗血小板剤、血栓溶解剤を投与中の患者(「相互作用」の項参照)　(2)月経期間中の患者[出血傾向を助長するおそれがある。]　(3)出血傾向並びにその素因のある患者[出血傾向を助長するおそれがある。]
**2.重要な基本的注意**　(1)本剤の有効成分は「ケアロードLA錠60μg」、「ベラサスLA錠60μg」と同一であるが、原発性肺高血圧症において用法・用量が異なることに注意すること。(2)原発性肺高血圧症において「ケアロードLA錠60μg」、「ベラサスLA錠60μg」から本剤へ切り替える場合には、「ケアロードLA錠60μg」、「ベラサスLA錠60μg」の最終投与時から12時間以上が経過した後に、本剤をベラプロストナトリウムとして原則1日60μgを3回に分けて食後に経口投与することから開始すること。また、「ケアロードLA錠60μg」、「ベラサスLA錠60μg」と同用量の本剤に切り替えると、過量投与になるおそれがあるため注意すること。
**3.相互作用　併用注意(併用に注意すること)**　抗凝血剤(ワルファリン等)、抗血小板剤(アスピリン、チクロピジン等)、血栓溶解剤(ウロキナーゼ等)、プロスタグランジンI₂製剤(エポプロステノール、ベラプロスト[注1])、エンドセリン受容体拮抗剤(ボセンタン)
注1)同一有効成分を含有する「ケアロードLA錠60μg」、「ベラサスLA錠60μg」等との併用に注意すること。
**4.副作用**　○**慢性動脈閉塞症に伴う潰瘍、疼痛及び冷感の改善**　総症例7,515例中、370例(4.9%)に副作用(臨床検査値異常を含む)が認められ、その主なものは頭痛91例(1.2%)、顔面潮紅60例(0.8%)、ほてり39例(0.5%)、下痢29例(0.4%)、嘔気20例(0.3%)等であった。　(再審査結果通知:1999年3月)
○**原発性肺高血圧症**　肺高血圧症の臨床試験において総症例40例中、24例(60.0%)に副作用(臨床検査値異常を含む)が認められ、その主なものは頭痛9例(22.5%)、LDH上昇5例(12.5%)、ビリルビン上昇4例(10.0%)、ほてり3例(7.5%)、下痢3例(7.5%)、嘔気3例(7.5%)、トリグリセライド上昇3例(7.5%)等であった。
(効能追加時:1999年9月)
使用成績調査において総症例244例中、57例(23.4%)に副作用(臨床検査値異常を含む)が認められ、その主なものは頭痛15例(6.1%)、AST(GOT)上昇9例(3.7%)、ALT(GPT)上昇8例(3.3%)、ほてり8例(3.3%)、顔面潮紅4例(1.6%)、倦怠感4例(1.6%)等であった。このうち、小児(15歳未満)については66例中、14例(21.2%)に副作用(臨床検査値異常を含む)が認められ、その主なものは鼻出血3例(4.5%)、AST(GOT)上昇3例(4.5%)、ALT(GPT)上昇3例(4.5%)、頭痛2例(3.0%)、ほてり2例(3.0%)等であった。(再審査申請時)
**(1)重大な副作用　1)出血傾向[脳出血**(0.1%未満)、**消化管出血**(0.1%未満)、**肺出血**(0.1%未満)、**眼底出血**(0.1%未満)]:観察を十分に行い、異常が認められた場合には投与を中止し、適切な処置を行うこと。 **2)ショック**(0.1%未満)、**失神**(0.1%未満)、**意識消失**(0.1%未満):ショック、失神、意識消失を起こすことがあるので、観察を十分に行い、血圧低下、頻脈、顔面蒼白、嘔気等が認められた場合には投与を中止し、適切な処置を行うこと。 **3)間質性肺炎**(頻度不明[注2]):間質性肺炎があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止し、適切な処置を行うこと。 **4)肝機能障害**(0.1%未満):黄疸や著しいAST(GOT)、ALT(GPT)の上昇を伴う肝機能障害があらわれることがあるので、観察を十分に行い、このような場合には投与を中止し、適切な処置を行うこと。 **5)狭心症**(頻度不明[注2]):狭心症があらわれることがあるので、異常が認められた場合には投与を中止し、適切な処置を行うこと。 **6)心筋梗塞**(頻度不明[注2]):心筋梗塞があらわれるとの報告があるので、異常が認められた場合には投与を中止し、適切な処置を行うこと。注2)自発報告によるものについては頻度不明。

**【承認条件】**
原発性肺高血圧症において可能な限り、再審査期間中の全投与症例を使用成績調査の対象とすること。なお、予後に関する成績も収集すること。

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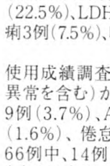

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